

LETTERS TO THE EDITOR

A novel de novo point mutation in the GTP cyclohydrolase I gene in a Japanese patient with hereditary progressive and dopa responsive dystonia

Hereditary progressive dystonia is characterised by lower limb dystonia of childhood onset with marked diurnal fluctuation and shows a dramatic and stable response to low dose levodopa. The disease is transmitted in autosomal dominant inheritance, and Segawa *et al*¹ proposed hereditary progressive dystonia as a new disease entity in the early 1970s. Dopa responsive dystonia, which was first proposed by Nygaard *et al*² in 1988, is essentially identical to hereditary progressive dystonia although it may include some other heterogeneous dystonias. The GTP cyclohydrolase I (GTP-CH I) gene on chromosome 14 is the causative gene of hereditary progressive/dopa responsive dystonia³ and more than 20 different mutations have been reported. We report a novel non-sense mutation in the GTP-CH I gene in a genetically confirmed sporadic Japanese patient.

A 12 year old Japanese girl developed gait disturbance with a dystonic pes equinovarus posture in the right leg at the age of 4 years. These symptoms showed diurnal fluctuation; they were mild in the morning and worsened later in the day, and sleep improved the symptoms. They dramatically and continuously responded to low dose levodopa/

carbidopa (100 mg/day) without adverse effects. Other members of her family, comprising the parents and one sister, had no symptoms.

Blood specimens of the patient and of the parents and sister were available for genetic analysis. For mutation analysis, genomic DNA was extracted from EDTA anticoagulated peripheral blood. Fragments of DNA containing the entire coding region of the GTP-CH I gene were obtained from genomic DNA by polymerase chain reaction (PCR) according to the method of Ichinose *et al*.³ Direct nucleotide sequencing of PCR products was performed with an automated DNA sequencer (Applied Biosystems 310) using the same primers as were used for amplification.

Direct nucleotide sequencing of genomic DNA of the patient showed a G to A transversion in exon 1 of the GTP-CH I gene (data not shown). This mutation produces a substitution of the tryptophan residue (TGG) with a stop codon (TGA) at position 96, which creates a new Eco57I cleavage site. The sequencing of the parents and the sister of the patient showed no mutation. To confirm the mutation, exon 1 was amplified and digested by Eco57I in all the four subjects. The restriction fragment length polymorphism consisted of two fragments (370 and 132 bp) in the mutant allele and one fragment (502 bp) in the normal allele (figure). The restriction pattern in the patient was consistent with heterozygous status, consisting of one each of the mutant and normal alleles, whereas that of the parents and sister, with homozygous status of two normal alleles. No other mutations were detected in the coding region of the gene.

The patient presented with typical clinical features of hereditary progressive dystonia. A new mutation in the GTP-CH I gene of the present patient causes a stop codon, and this mutation is most likely the pathogenic mutation. GTP-CH I catalyses the initial and rate limiting steps of tetrahydrobiopterin synthesis. Tetrahydrobiopterin is an essential cofactor for tyrosine hydroxylase, the rate limiting enzyme in the dopamine synthesis pathway. GTP-CH I activity in patients with hereditary progressive dystonia is less than 20% of that in normal subjects.³ The non-sense mutation in exon 1 confirmed in the present patient would have caused premature truncation of the GTP-CH I protein with a loss of an estimated 60% of the amino acid residues from the C terminal, and GTP-CH I activity, though it was not measured, may have been reduced below the critical threshold. To date, 22 different mutations in the GTP-CH I gene have been identified worldwide, and there seems to be no evidence of the founder effect.

To our knowledge, only a single case (patient 2 of Furukawa *et al*)⁴ was confirmed to be genetically sporadic. They identified the G to A transversion at the splice acceptor site of intron 1 in the GTP-CH I gene, causing skipping of the entire exon 2 in the mature mRNA. In the present family, the mutation was confirmed in the proband only, and not in the parents and the sister. The restriction fragment length polymorphism generated by Eco57I consisted of one fragment (502 bp) common to the parents and sister and an additional two fragments (370 and 132 bp) unique to the patient. The present patient was thus confirmed to be genetically sporadic and heterozygous, and is the second report of de novo mutation in the GTP-CH I gene.

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RYOGEN SASAKI
YUTAKA NAITO
SHIGEKI KUZUHARA

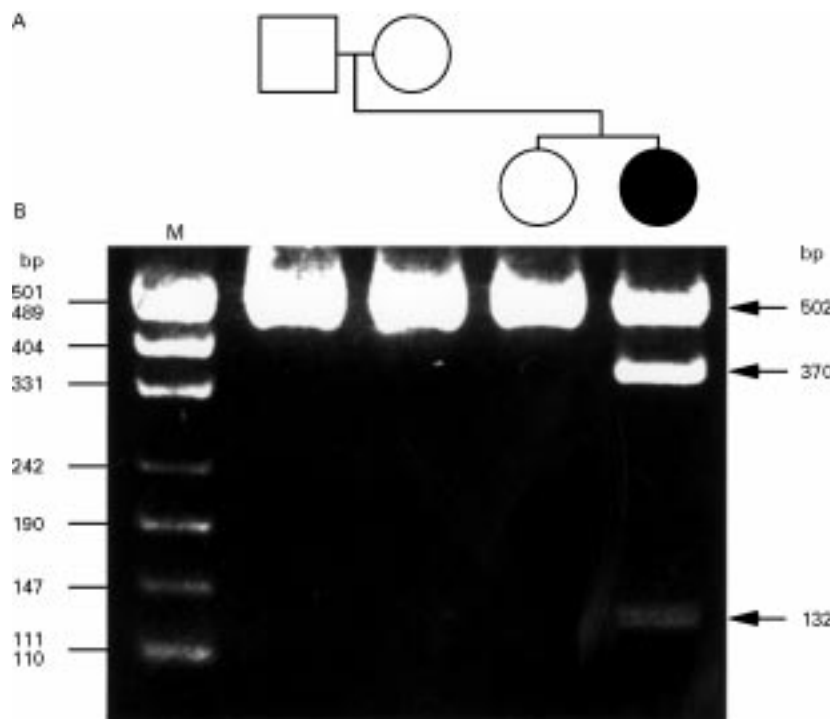
Department of Neurology, Mie University School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan

Correspondence to: Dr Ryogen Sasaki, Department of Neurology, Mie University School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan. Telephone 0081 59 232 1111; fax 0081 59 231 5082.

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Central nervous system involvement in four patients with Charcot-Marie-Tooth disease with connexin 32 extracellular mutations

In a recent issue of this *Journal*¹ there was a report of two cases of multiple sclerosis with duplicated CMT1A. Here we present four additional patients with Charcot-Marie-



(A) Pedigree of a Japanese hereditary progressive/dopa responsive dystonia family with mutation in the GTP-CH I gene. The affected proband is represented by solid symbol, and unaffected family members, by open symbols. (B) Agarose gel electrophoresis of Eco57I restriction pattern in the exon 1 of GTP-CH I gene. PCR product (502 bp) including exon 1 of the GTP-CH I gene from the patient was partially digested into two fragments of smaller sizes (370 and 132 bp) due to a Eco57I cleavage site created by a mutation in exon 1 of the gene. The 502 bp fragments from the unaffected family members remained undigested. Lane M=pUC19 DNA MspI digestion marker.

Tooth disease with CNS involvement as shown by electrophysiological studies and the presence of myelin lesions in brain MRI. In our patients point mutations were identified in GJB1, a gene coding for connexin 32 (GenBank acc number 117688). We also point to the possible importance of the position (intracellular or extracellular) of the mutations in the involvement or not of the CNS.

In the process of investigating a panel of patients with Charcot-Marie-Tooth disease for mutations leading to the disease, we have screened the GJB1 gene for mutations in six patients (C12, C64, C10, and C13 (all unrelated), and C2-1 and C2-2 (brothers) who did not have a CMT1A duplication and had a family history compatible with an X linked mode of transmission. GJB1 is a gene coding for connexin 32 (Cx32), a gap junction protein that is found in both the peripheral and the central nervous systems² and that has been reported by many to be responsible for CMTX, the X linked subtype of Charcot-Marie-Tooth disease. We performed our search using SSCP and nucleotide sequencing when additional bands were detected.³ Mutations leading to amino acid sequence changes and transmitted with the disease were detected in all six patients, whereas these nucleotide variations were not detected in 150 healthy control X chromosomes. Because Cx32 is a protein expressed in both the peripheral and the central nervous systems we proceeded to test for CNS involvement in those patients using electrophysiological (table) and MRI techniques. The clinical and laboratory findings for our patients were as follows.

Patient C2-1, a 19 year old man, had a history of 5 hour to 3 day long episodes of weakness—generalised or at other times localised to the left or right half of the body—dysarthria, and difficulty in swallowing. Neurological clinical examination showed muscle weakness and peripheral atrophy of the limbs, absence of tendon reflexes, distal loss of vibration in the legs, indifferent plantar response, and bilateral pes cavus. The CSF was normal. Brain SPECT (Tc-99m HMPAO {15 mCi}) showed significant reduction of blood flow in the left parietal lobe. Brain MRI showed bilateral symmetric areas in the central white matter supraventricularly with high intensity signal in T2 weighted

images. Electrophysiological studies (table) showed that both the central and peripheral nervous systems were affected. The patient had a C to T transition at position 164 (novel mutation).

Patient C2-2, the 21 year old brother of C2-1, had the same symptoms (multiple episodes of muscle weakness) since the age of 10 years. The clinical findings were also the same. In this case the CSF showed IgG oligoclonal bands. Brain MRI was normal. Electrophysiological studies also showed that both the central and peripheral nervous systems were affected. The patient had the same mutation as his brother C2-1, as was expected.

Patient C12, a 63 year old man, had progressive muscle weakness and peripheral atrophy of the extremities since the age of 9 years. When admitted he had severe muscle weakness, absence of tendon reflexes, distal loss of vibration in the legs, dysmetria, fine tremor, positive Romberg's sign, and bilateral pes cavus. The CSF showed an IgG index of 1.0 (normal<0.85) and oligoclonal bands. Brain MRI showed foci of demyelination in the white matter of the cerebral hemispheres. Electrophysiological studies also showed that both the central and peripheral nervous system were affected. The patient had the same mutation as patient C2-1.

Patient C64, a 58 year old man, presented with progressive muscle weakness and peripheral atrophy since the age of 10 years. His CSF was not sampled. Brain MRI showed high density areas of demyelination in the white matter on the left side in the frontoparietal area. The patient had a G to A transition at position 491 (novel mutation).

Patient C10, a 78 year old man, presented with progressive muscle weakness and peripheral atrophy of the legs since the age of 11. The clinical picture was the same as that of patient C64. The CSF and brain MRI were normal. The patient had a T to A transition at position 359 (novel).

Patient C13, a 40 year old man, presented with progressive muscle weakness and peripheral atrophy starting at the age of 7 years. His CSF and brain MRI were normal. The patient had a C to T transition at position 43 (already reported⁴). Sural nerve biopsy performed in patients C2-1, C2-2, C64, and C10 showed loss of muscle fibres and "onion bulb" formation. It is of particular interest,

possibly implying an underlying mechanism, that the four patients with evidence of CNS involvement (C2-1, C2-2, C12, and C64) had mutations in the extracellular domain of Cx32, and by contrast, in the two patients with no evidence of CNS involvement (C10, C13) the mutations were in the intracellular domain of the protein.

The exact pathogenetic mechanisms of the various types of myelin damage are not yet fully understood. Therefore, we cannot reach any convincing conclusions about the possible relations between those degenerative processes and the position of Cx32 mutations. However, we hope that our findings will contribute to a better understanding of some myelin damage mechanisms.

MARIOS PANAS
CHARALAMBOS KARADIMAS
DIMITRIS AVRAMOPOULOS
DEMETRIS VASSILOPOULOS
*Clinical and Molecular Neurogenetics Unit,
Department of Neurology of Athens National
University (Eginition Hospital), Greece*

Correspondence to: Professor Demetris Vassilopoulos, Department of Neurology of Athens National University (Eginition Hospital), 74 Vas. Sophias Av. Athens 115 28, Greece tel.-fax: x30-1-7244917.

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Lack of mutation G209A in the α -synuclein gene in French patients with familial and sporadic Parkinson's disease

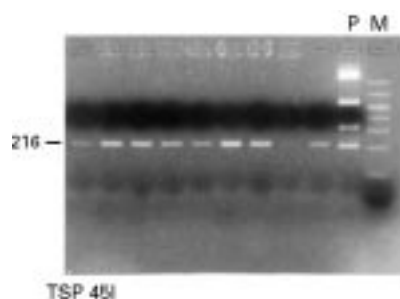
Polymeropoulos *et al* described the genetic linkage of a large Italian Parkinson's disease pedigree (Contursi) to chromosome 4q21-q23¹; more recently the sequence of the α -synuclein gene located in this chromosomal region in affected patients from this kindred disclosed that most of the affected members were heterozygous for a missense mutation (alanine→threonine) at position 53 of the protein.² This same missense mutation was also found in three additional unrelated families of Greek origin with Parkinson's disease.

The mutation was found by DNA sequence analysis of the fourth exon of the α -synuclein gene, disclosing a single base pair change at position 209 from G to A (G209A), and creating a novel *Tsp45I* restriction site. Using a polymerase chain reaction (PCR) assay and *Tsp45I* restriction, we have found some French patients with Parkinson's disease. Genomic DNA was amplified with primers 3 and 13 of the DNA sequence (GenBank ID U46898) in a 50 μ l reaction volume (10 mM Tris-HCl, pH=8.3; 50 mM KCl; 1.5 mM MgCl₂; 200 μ M of each dNTP and 1 U *Taq* polymerase); cycling parameters were: one initial step of hybridisation at 94°C during 5 minutes, 35 cycles of PCR (hybridisation at 60°C, 40 seconds, extension at 72°C, 40 seconds; denaturation at 94°C, 40 seconds) and a final extension step (5 minutes at 74°C). A 20 μ l aliquot of the 216 base pair (bp) product was restricted with the

Electrophysiological data from the six patients

		C2-1	C2-2	C12	C64	C10	C13	Normal
MNC:								
Median	Ampl (mV)	4	0.8	0.6	0.8	1.0	0.2	
	DL (ms)	4.6	4.4	6.6	5.7	4.8	8.6	
	CV (m/s)	36	33	29	31	29	21	
Peroneal	Ampl (mV)	2.5	0.4	NE	NE	NE	NE	
	DL (ms)	7.4	5.1	NE	NE	NE	NE	
	CV (m/s)	38	30	NE	NE	NE	NE	
SNC:								
Sural	Ampl (mV)	2	4	NE	0.5	NE	NE	
	DL (ms)	3.6	2.9	NE	8.1	NE	NE	
	CV (m/s)	31	31	NE	22	NE	NE	
BAERs:								
Right	I (ms)	1.58	2.20	1.82	1.68	1.52	1.41	<1.73
	III (ms)	4.54	4.58	4.63	4.61	3.12	2.89	<3.79
	V (ms)	6.14	7.22	6.87	6.24	5.25	4.97	<5.72
Left	I (ms)	1.72	1.62	1.98	1.85	1.43	1.51	<1.73
	III (ms)	4.24	4.60	4.75	4.79	2.98	3.13	<3.79
	V (ms)	6.20	6.22	7.31	6.87	4.95	4.87	<5.72
VEPs:								
Right	Lat (ms)	111.5	95.5	NP	112.2	NP	NP	80-108
	Lat (ms)	97	110	NP	110.8	NP	NP	R-L<8

MNC=Motor nerve conduction; Ampl=amplitude; DL=distal latency; CV=conduction velocity; SNC=sensory nerve conduction; BAERs=brain stem auditory evoked responses; waves I, III, and V; VEPs=visual evoked potentials; Lat=latency; NE=not evoked; NP=not performed.



Electrophoresis patterns of *Tsp45I* digestion of polymerase chain reaction (PCR) products. Lane P shows pUC19 plasmid restricted by the enzyme (the four restriction fragments at 1583, 576, 311, and 211 bp). All the nine subjects tested were wild type, producing a single 216 bp PCR product which was resistant to *Tsp45I* digestion. M=DNA size marker.

Tsp45I enzyme at 65°C for 5 hours; the efficiency of the *Tsp45I* restriction was verified by monitoring for the pUC19 plasmid restriction (four fragments at 1588, 576, 31, and 211 bp). The digested PCR products were separated by electrophoresis on a 3% agarose gel and visualised by ethidium bromide staining.

Fourteen French families^{3,4} with at least two members in each family meeting clinical criteria for idiopathic Parkinson's disease were tested. Affected members in all families exhibited at least two of the three cardinal signs of Parkinson's disease (bradykinesia, rigidity, and resting tremor), as well as marked improvement with levodopa treatment. The G209A mutation was not found in 27 patients with Parkinson's disease belonging to these 14 French pedigrees. The *Tsp45I* restriction site was also absent in the genomic amplificate of 79 patients of French origin with sporadic Parkinson's disease.

We conclude that the G209A mutation is rare, or absent, in French patients with familial and sporadic Parkinson's disease, and similar results were obtained recently from American patients.⁵ The main age at onset of disease in our patients with Parkinson's disease, both familial and sporadic, was 64.5 (range 25–88) years. The major kindred published² in which the G209A mutation was found originates in Contursi (southern Italy) and has fairly typical Parkinson's disease, albeit with relatively early onset of symptoms and rapid subsequent progression; little has been reported until now about the three Greek families with Parkinson's disease with the G209A mutation, except that they too have relatively early onset. Probably the G209A mutation concerns a small set of families with Parkinson's disease, originating from some focal localities on the Mediterranean coast.

G LUCOTTE
G MERCIER
J C TURPIN

Laboratory of Molecular Neurogenetics, Maison
blanche Hospital, Reims 51092, France

Correspondence to: Professor G Lucotte, Laboratory of molecular neurogenetics (Service of Neurology), Maison Blanche Hospital, 45 rue Cognacq-Jay, 51092 Reims, France.

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Resolution of extensive spinal epidural haematoma with conservative treatment

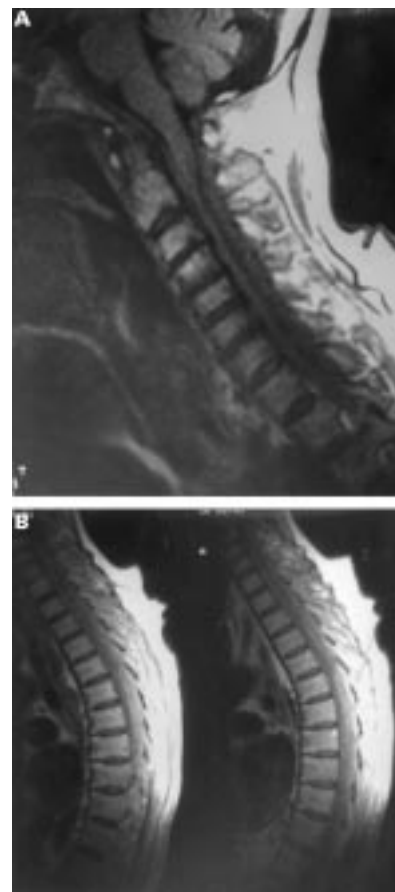
Spontaneous spinal epidural haematoma (SSEDH) is an uncommon condition presenting with local and radicular pain associated with clinical features of rapidly progressive spinal cord compression. The cause of the bleeding is varied, with anticoagulant therapy recognised to be the commonest known aetiological factor.¹ Surgery is the preferred treatment, regardless of aetiology, especially in patients with extensive haematomas and neurological deficits.^{1,2} Spontaneous resolution of the haematoma is reported but rare.^{3–5} We report a case of an extensive spontaneous spinal epidural haematoma extending from the upper cervical to lower thoracic region secondary to anticoagulant therapy, with remarkable clinical and radiological improvement with conservative management.

An 82 year old woman was admitted with a one week history of neck pain and upper thoracic pain, which had worsened during the preceding 4 days. On the day before admission, she developed sudden onset of complete paraplegia with urinary retention. She had noticed some improvement in power in her legs and back pain on the day of referral to our institution. She has a medical history of ischaemic heart disease with congestive cardiac failure and was on long term warfarin therapy for atrial fibrillation. At the referring hospital, her international normalised ratio (INR) was 10 and she was transferred to our neurosurgical unit after vitamin K and fresh frozen plasma were administered.

When assessed on arrival, she was complaining of mild thoracic pain. There was no neurological abnormality in the upper limbs. Tone was increased in the lower limbs with grade 2 (MRC) power on the left and grade 3 on the right. She had sensory loss to pin prick below D10 with saddle anaesthesia. Posterior column sensation was preserved. Deep tendon reflexes were pathologically brisk in the lower limbs and planter responses were extensor bilaterally.

Her INR was 1.9 and radiography of the cervical spine showed spondylotic changes and thoracic spine radiography showed evidence of osteoporosis. There was no fracture. Brain MRI showed an intermediate to high signal intensity epidural lesion suggestive of haematoma from C-1 extending to the lower thoracic region, compressing the dorsal aspect of the cord (figure).

As the power in her lower limbs was improving, we elected to treat her conservatively. Her clotting derangement was corrected with vitamin K and fresh frozen plasma while monitoring her INR. Her power continued to improve and at the time of her discharge she had grade 4 power in her legs with associated mild distal sensory loss. Eight weeks later, she had grade 5 power but was slightly unsteady on her feet due to spasticity. Sensory testing was normal. Repeat MRI showed almost complete resolution of the haematoma.



Cervical and thoracic MRI showing the extent of epidural haematoma.

Spontaneous spinal epidural haematoma (SSEDH) is an uncommon disorder first described by Jackson in 1869. It usually affects patients in the age group 20 to 70 and the thoracic spine is the commonest region affected. Spinal MRI is the investigation of choice in establishing diagnosis, characteristically showing increased signal intensity in T1 weighted images in an epidural mass at the first examination or increasing signal intensity with time; and in T2 weighted images, showing focal low signal intensity in early stages.⁴ The aetiology includes vascular malformations, coagulopathies, anticoagulant therapy, aspirin intake, minor trauma and hypertension.^{1,2,6} In about 40% of cases, the cause is unknown despite extensive investigations.¹ About 300 cases of SSEDH have been reported in the world literature.^{1–6} Anticoagulant therapy is the commonest known cause of SSEDH,¹ but prothrombin time or INR values do not seem to correlate with the risk of haemorrhage.^{1,6}

Surgery is generally the treatment of choice as the rapid decompression of the spinal cord ensures maximal neurological recovery. It is generally held that early (<12 hours) surgery and good preoperative neurological status promise the best possible outcome, although delayed surgery after total loss of spinal cord function does not completely exclude the possibility of some recovery.^{1–3}

We report a case of SSEDH in an 82 year old lady who was on anticoagulant therapy (warfarin), for cardiovascular disease, and presented with features of spinal cord compression associated with back pain. Spinal MRI disclosed spinal epidural haematoma extending from C-1 to the lower thoracic

region. Such an extensive haematoma is very uncommon.¹⁻⁴ Literature review suggests that SSEDH involving more than two vertebral levels carries a worse prognosis.^{1,2} Hence, the rapid recovery seen in our patient despite such an extensive haematoma is remarkable.

Improving clinical condition, extensive haematoma, age, and poor medical condition of the patient prompted us to pursue conservative treatment with good clinical and radiological improvement. Although emergency surgery is the treatment of choice, non-surgical therapy in the medically unfit, patients with minor deficits, and in patients with initial clinical improvement, has yielded good results, in all the aetiological groups,^{1,3,4} which fits with our experience. Fresh frozen plasma, Vitamin K, and monitoring of INR have been the mainstay of conservative treatment in patients on anticoagulants, who need repeat MRI for follow up.^{3,4} With the ever increasing number of patients on anticoagulant therapy for cardiovascular diseases, SSEDH is likely to become a more common problem. When to restart anticoagulant therapy and the optimal INR values to be maintained after restarting are the questions still unanswered in the literature.

In summary, SSEDH in patients taking anticoagulant drugs with initial clinical improvement may be successfully treated with regular clinical, haematological, and MRI monitoring even if they have extensive clots.

RAVI KUMAR
CHRISTOPHER GERBER

Department of Neurosurgery, Regional Neurosciences
Centre, Newcastle General Hospital,
Newcastle upon Tyne, UK

Correspondence to: Mr Christopher Gerber, Department of Neurosurgery, Regional Neurosciences Centre, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, UK.

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Flail arm syndrome: a distinctive variant of amyotrophic lateral sclerosis

In a retrospective case note study of patients referred to a specialist clinic for motor neuron disorders we identified a subgroup of patients with severe wasting and weakness of the arms without significant functional involvement of other regions. This "flail arm syndrome" was identified in 39/395 (10%) of the subjects studied. Their clinical characteristics were compared with the amyotrophic lateral sclerosis (ALS) group as a whole. The age of onset was similar between the two groups but the male:female ratio was 9:1 in the flail arm group, compared with 1.5:1 in the ALS group ($p=0.0015$). Although there was a trend

towards improved survival in the flail arm group (median survival 57 (95%CI 45-69) months) compared with the ALS group (39 (95%CI 35-43) months), this did not reach significance ($p=0.204$) and was not an independent prognostic factor. As many patients with flail arm syndrome develop upper motor neuron signs in the lower limbs this syndrome probably represents a variant of ALS. It seems likely that unknown factors linked to male sex predispose a proportion of patients to develop the flail arm phenotype.

Historically, physicians have categorised illnesses according to their clinical characteristics. As a result the adult sporadic motor neuron disease syndromes have been described according to the site of lesion onset. Most patients present with both upper and lower motor neuron signs in the limbs (classic motor neuron disease or ALS). Rarer forms of predominantly upper and lower motor neuron syndromes are also recognised (primary lateral sclerosis and progressive muscular atrophy respectively). We have noted that a subgroup of patients with classic ALS present with progressive wasting and weakness of the arms, with little or no functional impairment of the bulbar muscles or legs (figure). Here we describe their clinical features and natural history in comparison to the ALS group as a whole. We have used the term "flail arm syndrome" to describe this variant of ALS.

All patients attending our specialist motor neuron disorders clinic between 1 January 1990 and 30 September 1996 were studied in a retrospective case notes study. Patients with alternative diagnoses, such as Kennedy's disease, spinal muscular atrophy, and multifocal motor neuropathy were excluded after full genetic, neurophysiological, and serological investigation, leaving 395 patients with a firm diagnosis of ALS. The censoring date for survival analysis was 31 January 1996.



Patients were classified according to the El Escorial criteria¹ and included in a detailed database incorporating key characteristics of the disease. Most fulfilled probable or definite ALS El Escorial categories having upper and lower motor neuron signs at first review. A minority with predominantly lower motor neuron features at presentation fulfilled suspected or possible ALS El Escorial categories. The flail arm syndrome was defined as a predominantly lower motor neuron disorder of the upper limbs without significant functional involvement of other regions at clinical presentation. Specifically, the wasting and weakness of the upper limbs had to be profound, symmetric, and involve proximal muscle groups (MRC grade ≤ 3). Those fulfilling the flail arm criteria were identified and compared with the rest of the ALS population based on the clinical assessment made at the time of the first clinic visit. Follow up was complete.

Demographic variables were compared using Student's t test. The χ^2 test and linear regression were used to test the independence of two variables. Survival of patients with ALS was estimated using the Kaplan-Meier curves and the log rank test was used to compare different categories. The Cox proportional hazards model was used to assess the simultaneous effects of several variables on survival. Results are expressed as the mean ± 1 SD and a p value of <0.05 was considered significant.

Of 395 patients, 39 (10%) were identified as having the flail arm syndrome. Nine out of 39 (23%) of the patients with the syndrome had solely lower motor neuron features at the time of presentation. Upper motor neuron signs in the legs were present in most patients (77%) and although bulbar signs were present in 22 (56%) during the follow up period they were commonly asymptomatic at presentation.



(A) This 54 year old man with the flail arm syndrome has severe wasting of the arms causing profound weakness. Note the symmetric distribution and involvement of proximal musculature. Muscle bulk and strength were relatively preserved in the legs but lower limb reflexes were pathologically brisk and the plantar responses extensor. (B) Note the very similar pattern of wasting in a patient with "progressive muscular atrophy" depicted in a 1888 text of Gowers.²

The male to female ratio was strikingly different between the two groups, being 9:1 in the flail arm group and 1.5:1 in the ALS group (Student's *t* test, $p=0.0015$). The mean age of symptom onset was similar (flail arm 58 (SD 13) years and ALS 55 (SD12) years) and there was no significant difference in the duration of follow up (flail arm 24 (SD 17) months and ALS 20 (SD 13) months, $p=0.17$) or the proportion of familial cases (both 9%).

Using Kaplan-Meier analysis, the median survival in the flail arm group was 57 (95%CI 45–69; range 6–109) months, compared with 39 (95%CI 35–43; range 2–577) months in the ALS group, but this did not reach significance (log rank test, $p=0.204$). There was no significant difference between the mean survival of flail arm and limb onset ALS groups. Using the Cox proportional hazards model, the flail arm syndrome was not identified as an independent risk factor determining survival.

The features of this distinctive ALS variant have not previously been characterised but it was probably first described by Gowers in his 1888 text *Diseases of the Nervous System*. In the chapter on the progressive muscular atrophies he noted that “when the arms are the seat of (such) atrophy as has been described, the legs, if not also wasted, may be normal, but they are often paralysed without being wasted” suggesting a pyramidal lower limb weakness.² Indeed, the illustration of a patient with primary muscular atrophy depicts the typical appearance of the patient with flail arm syndrome.

The predominant clinical feature of this syndrome is the relatively symmetric and proximal involvement of both arms, causing severe wasting and functional disability, with little or no weakness of the leg or bulbar musculature. Signs of corticospinal tract involvement are common in the legs and although denervation may be present in other regions this pattern of flail arms may persist for many years. Despite a severe loss of motor neurons in the cervical cord of patients with flail arm syndrome the higher cervical segments innervating the diaphragm seem to be spared early in the course of the disease.

What is the relation between the flail arm syndrome and other forms of ALS? The demonstration of upper motor neuron signs in most patients distinguishes this syndrome from primary muscular atrophy although there is probably an overlap. Our findings suggest that in most instances the flail arm syndrome represents a variant of classic ALS and most patients fulfil the probable or definite ALS El Escorial categories.¹ Although our clinic based ALS population is selected by referral it seems to be broadly representative judging by the demographic features described in other clinic and population samples.^{3,4}

We, and others, have previously reported the influence of genotype on ALS phenotype with the apolipoprotein E $\epsilon 4$ allele being associated with a bulbar onset of disease.^{5,6} It is interesting to note that whereas the male:female ratio in most studies is around 1.5:1 for ALS overall, women predominate in the late onset bulbar palsy group.^{3,4} The most striking finding of our study is the predominance of males in the flail arm group with a ratio of 9:1. It may be that factors linked to male sex predispose a proportion of patients to develop the flail arm phenotype. Curiously a male preponderance is also described in other lower motor neuron syndromes such as

multifocal motor neuropathy and monomelic amyotrophy.^{7,8}

We suspect that survival of patients with flail arm syndrome might be better than those with other forms of ALS as the median survival in the flail arm group was 57 months, compared with 39 months in the ALS group. Although the difference was not significant, our numbers are still small and larger studies are needed. We conclude that the flail arm syndrome is a distinctive clinical variant of ALS that is strikingly more common in males and may have a better prognosis.

M T M HU
C M ELLIS
A AL-CHALABI
P N LEIGH
C E SHAW

Department of Clinical Neuroscience, Institute of Psychiatry and King's College School of Medicine and Dentistry, London, UK

Correspondence to: Dr CE Shaw, Department of Clinical Neuroscience, Institute of Psychiatry and King's College School of Medicine and Dentistry, London SE5 8AF, UK. Telephone 0044 171 346 5182; fax 0044 171 346 5181; email spgtces@iop.bpmf.ac.uk

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Multifocal cortical myoclonus and cerebral amyloid β -peptide angiopathy

The commonest clinical presentations of the sporadic cerebral amyloid angiopathies are with either recurrent lobar haemorrhages or with dementia.¹ In addition, transient focal neurological syndromes have occasionally been reported in association with cerebral amyloid angiopathies. These may represent transient ischaemic events or possibly focal seizures related to petechial intraparenchymal haemorrhages which are not associated with neuroimaging abnormalities; large haemorrhages may follow the onset of transient symptoms by weeks or months.^{2,3} We report on a patient with multifocal cortical myoclonus who subsequently proved to have amyloid β -peptide cerebral amyloid angiopathy, an association not previously described. We consider possible pathogenetic interrelations of these findings.

A 65 year old woman presented with a 4 year history of involuntary movements. She had been noted to have abnormal jerking movements of her legs—for example, when climbing the stairs—which, on occasion had caused her to fall. Using an electric vacuum

cleaner or hearing the telephone ring had been noted to trigger these involuntary movements. There was no history of cognitive impairment. Her medical history was unremarkable aside from treated hypothyroidism. Family history was positive for sudden death, all three of her elder siblings (one sister, two brothers) dying in their mid-60s. One had previously had angina, the other two had been healthy until the time of their deaths, which were ascribed to a “heart attack” and a “clot on the brain”, respectively.

Examination of the patient disclosed a pronounced startle response, and action myoclonus in all limbs. There was no consistent stimulus sensitivity of the jerks. Otherwise, neurological examination was within normal limits.

Investigations, which proved either normal or negative, included standard tests of haematological and biochemical indices, thyroid function tests, serum vitamin B₁₂, red cell folate, serum electrophoresis, quantitative immunoglobulins, angiotensin converting enzyme (ACE) concentrations, autoantibodies (including ANCA, anti-endothelial antibodies, and anti-GAD antibodies), and anti-neuronal antibodies (Hu, Purkinje). Blood film was negative for acanthocytes. Analysis of CSF showed a raised protein (0.82 g/l) but normal glucose concentration, cytology, and ACE; oligoclonal bands were not present. T2 weighted brain MRI showed a few small foci of high signal in the periventricular white matter, thought to represent age related small vessel disease. Carotid angiography was normal. Small bowel biopsy showed a normal mucosa with no evidence of coeliac disease. Analysis of mitochondrial DNA for common mutations (positions 3243, 3271, 8344, and 8356) proved negative. Psychometric assessment showed the patient to have a verbal IQ of 94, performance IQ of 95, indicative of functioning in the lower half of the average range but within the patient's estimated average optimal level of ability. She was noted to show signs of inefficiency and slowness, particularly in word retrieval and frontal lobe tasks, but there was no unequivocal evidence of focal deficits.

Peripheral, cervical, and cortical somatosensory evoked potentials after electrical stimulation of the median nerve at either wrist were of normal latency and morphology. However, although the amplitude of peripheral and cervical potentials was normal, the cortical responses were abnormally large, particularly from the right arm (22 μ V; left 15 μ V). Hence, on clinical and neurophysiological grounds, a diagnosis of multifocal cortical myoclonus of unknown cause was made. The patient was treated with clonazepam (0.25 mg twice daily), with marked symptomatic benefit at follow up.

Ten months after these investigations, the patient presented to an ophthalmologist with episodes of metamorphopsia for which no ocular cause was found. A further 3 months later she presented with a sudden onset of right parietal headache associated with vomiting and left sided pyramidal signs. Brain CT disclosed a large right sided parieto-occipital intracerebral haematoma with mass effect. At surgical drainage of the haematoma, a small piece of brain tissue was removed from the right parieto-occipital region. Histological examination showed small, irregular fragments of cortical grey and minimal amounts of white matter. The first included vessels, some of which were in obvious continuity with meningeal vessels. Most of them had

thickened hyaline walls which stained with Congo red, showing the characteristic apple green birefringence under polarised illumination, and were positive with immunostaining for β A4. This immunostaining also showed diffuse plaques, a few containing cores most of which could not be seen on routine staining. No abnormalities were seen in the white matter. Silver impregnation (Bielschowsky) and tau immunohistochemistry did not show neurofibrillary tangles, neuritic plaques, or cortical dystrophic neurites. According to the criteria of the Boston Cerebral Amyloid Angiopathy Group,³ the histological findings and clinical data indicated a diagnosis of "probable cerebral amyloid angiopathy with supporting pathological evidence". DNA was screened by polymerase chain reaction amplification for the presence of mutations in the amyloid precursor protein (APP) gene, which are known to cosegregate with hereditary cerebral haemorrhage with amyloidosis Dutch type (HCHWA-D; codons 670/671 of exon 16 and in codons 692, 693, 713, and 717 of exon 17). No mutation was found.

The patient underwent psychometric reassessment 1 month after the intracerebral haemorrhage and surgical drainage, from which she had made a good physical recovery. In keeping with the location of the haemorrhage, she was found to have significantly impaired visual perceptual functions, with left unilateral neglect, an inability to discriminate shapes, and a severe deterioration in her performance on the visual version of the recognition memory test (verbal version remained within the average range). Additionally, a mild degree of verbal intellectual deterioration was noted (verbal IQ 83).

A wide variety of disorders may produce cortical myoclonus: the differential diagnosis includes anoxic injury, focal CNS damage (vascular or neoplastic lesions of sensorimotor cortex), encephalopathies (metabolic, mitochondrial, viral, paraneoplastic, toxic), degenerations (basal ganglia, spinocerebellar), malabsorption syndromes (coeliac disease, Whipple's disease), storage disorders, and dementias (Creutzfeldt-Jakob disease). Myoclonus may also be encountered in Alzheimer's disease, in which it is associated with increasing severity of dementia. We are not aware of previous reports of cortical myoclonus as a clinical feature of sporadic cerebral amyloid angiopathy. Although this could be a chance concurrence, it is possible that recurrent small intraparenchymal bleeds from angioathic vessels may have been causal, as vascular lesions are a recognised cause for cortical myoclonus. Another possibility which may be worth considering relates to the effects of amyloid β -peptide ($A\beta$) and its metabolic fragments on neuronal membrane ion channels and their associated currents.⁴ Because the pathophysiology of cortical myoclonus is thought to reflect both increased excitability and deficiency of inhibitory processes in the cortex,⁵ the effects of $A\beta$ on a variety of ion currents, both excitatory and inhibitory, might theoretically produce such an imbalance and hence contribute to the development of cortical myoclonus.

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A J LARNER

PAUL ELKINGTON

HITEN MEHTA

Department of Neurology

CORRADO D'ARRIGO

FRANCESCO SCARAVILLI

Department of Neuropathology

PETER RUDGE

Department of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Correspondence to: Dr AJ Larner, National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK. Fax 0044 171 829 8720.

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Antiganglioside antibodies in various episodes in a patient with recurrent Guillain-Barré syndrome

Guillain-Barré syndrome is defined as an acute, monophasic polyneuropathy. It recurs in 2%-5% of patients.¹ Both the initial and recurrent episodes are preceded by an infection. Antibodies against several gangliosides are often present in the acute phase in serum samples from patients with Guillain-Barré syndrome.² There have been no previous reports, however, on anti-ganglioside antibodies in patients with recurrent disease. We report finding anti-ganglioside antibodies in a patient with recurrent Guillain-Barré syndrome during the third and fourth episodes.

Ten days after a bout of upper respiratory tract infection, a 26 year old man noted paraesthesias in his fingers and toes, and rapidly developed limb weakness. He had bulbar palsy and areflexic tetraparesis on day 1, and underwent three sessions of plasmapheresis on days 3, 4, and 5. Disability was maximal on day 6. Bulbar weakness disappeared on day 8, and he could walk without support on day 14. He had had similar episodes of acute, monophasic paralytic disease at the ages of 14 and 19. Six years later, he experienced a fourth episode. Three days after an upper respiratory tract infection, he rapidly developed dysarthria, digital paraesthesias, and leg weakness. Neurological examination on day 2 showed bilateral external ophthalmoplegia, facial diplegia, and areflexic tetraparesis. He required mechanical ventilation from days 2 to 19, and underwent five sessions of plasmapheresis on days 2, 3, 4, 6, and 9, then intravenous immunoglobulin therapy from days 11 to 15. His disability began to lessen on day 11 and had disappeared by day 34.

An enzyme linked immunosorbent assay³ showed IgG antibody titres to GM1 (<500), GM1b (128 000), GD1a (128 000), GalNAc-GD1a (<500), GT1a (64 000), GD1b (4000), and GQ1b (32 000) on day 3 during the third episode. No IgM anti-ganglioside antibodies were detected. On day

113, during the recovery phase, the anti-ganglioside IgG titres were <500. Serum on day 3 of the fourth episode had IgG antibodies titres to GM1 (<500), GM1b (256 000), GD1a (128 000), GalNAc-GD1a (<500), GT1a (64 000), GD1b (1:4000), and GQ1b (1:64000). Thin layer chromatography with immunostaining⁴ confirmed that the IgGs in the acute, progressive phase of both attacks reacted with the same gangliosides (data not shown).

Differentiation between Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP) relies on the time needed to reach maximum disability. Our patient had four episodes of typical Guillain-Barré syndrome, not of CIDP. Neurological function in each episode reached a nadir within 2 weeks of onset and returned to normal within 5 weeks. The distinction between Guillain-Barré syndrome and CIDP, however, is blurred in the early onset phase in some patients. Protein concentrations in CSF in CIDP tend to remain raised during remission and at the onset of recurrence; whereas CSF protein concentrations are normal within 1 week of the onset of Guillain-Barré syndrome, which may provide a way of distinguishing it from CIDP.¹ Only low anti-ganglioside antibody titres, which were unlikely to have a role in the pathogenesis, were found in some patients with CIDP.⁵ The presence of high anti-ganglioside antibody titres at the onset of a recurrence may be of use in confirming the diagnosis of recurrent Guillain-Barré syndrome.

In recurrent Guillain-Barré syndrome, the nature of the antecedent illness usually tends to differ from episode to episode.¹ Our patient, however, had similar upper respiratory symptoms before each onset of neurological symptoms. Antecedent agents such as *Campylobacter jejuni* and cytomegalovirus have ganglioside epitopes,^{4,5} and therefore may produce the anti-ganglioside antibodies in Guillain-Barré syndrome.

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YUMI TAGAWA

NOBUHIRO YUKI

KOICHI HIRATA

Department of Neurology, Dokkyo University School of Medicine, Tochigi, Japan

Correspondence to: Dr Y Tagawa, Third Department of Internal Medicine, Kagawa Medical University, Ikenobe 1750-1, Miki, Kida, Kagawa 761-0793, Japan; fax: 81-87-891-2158, e-mail: ytagawa@kms.ac.jp

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Urinary retention associated with a unilateral lesion in the dorsolateral tegmentum of the rostral pons

The existence of a brainstem region concerned with micturition has been known since the report of Barrington more than 70 years ago.¹ In animals such a pontine micturition centre has been located in the dorsolateral tegmentum of the rostral pons, corresponding to Barrington's micturition centre,² but such a centre has not been precisely localised in humans. We describe a patient with presumed rhombencephalitis presenting with urinary retention and present his MRI findings. To our knowledge, this is the first MRI demonstration of a circumscribed lesion related to the putative pontine micturition centre in humans.

A 30 year old man with no history of voiding problems developed high fever, light headedness, frequent urination, and voiding difficulty. One day after onset, urinary retention occurred despite his sensation of needing to void. Two days later, in addition to urinary retention, the patient also had left cheiro-oral dysaesthesia and horizontal diplopia. Prostate examination did not show abnormalities. Urinary retention was managed with an indwelling catheter until 7 days after onset of his symptoms. The patient did not have a history of overdistension of the urinary bladder. Even though all his symptoms began to improve, the patient was referred to our hospital for an evaluation of neurological abnormalities.

Examination 9 days after onset showed mild right horizontal gaze paresis with intact vestibulo-ocular reflex, ipsilateral saccadic pursuit, and hypaesthesia around the left mouth angle and thumb and index finger, suggesting involvement of the right pontine tegmentum. Indeed, in addition to scattered amorphous lesions in the pons and cerebellum, brain MRI (1.5 tesla) showed a discrete lesion in the right upper pontine tegmentum

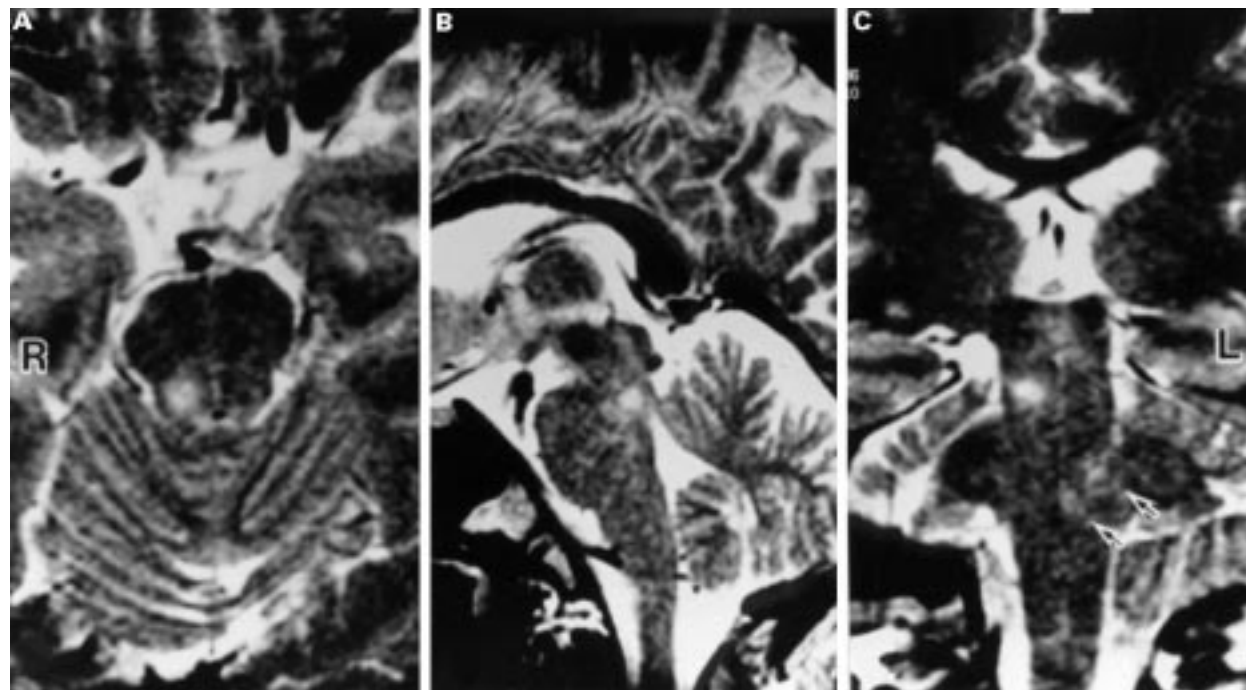
(figure). An MRI of the spinal cord disclosed no abnormal intensity areas. Lumbar puncture yielded CSF with normal cell counts (3/ μ l) and mildly increased protein (52 mg/dl). Neither oligoclonal bands nor myelin basic protein were present in the CSF; intrathecal IgG synthesis was within the normal range. Serum autoantibody and viral antibody tests did not contribute to diagnosis. A CO₂ cystometry with sphincter EMG 3 weeks after onset showed increased bladder volume over 555 ml and atonic cystometrogram (detrusor areflexia), despite the absence of subjective urinary symptoms. Organic obstructive urological disease was radiologically excluded. All neurological and MRI abnormalities cleared by 1 month after onset. One year follow up showed no recurrence of the neurological symptoms.

Based on neurological findings, the patient was thought to have incomplete involvement of the right paramedian pontine reticular formation, smooth pursuit pathway, and medial lemniscus, suggestive of a right pontine tegmental lesion. The association of acute and reversible urinary retention was consistent with a lesion in the rostral portion of the pontine tegmentum.³ Indeed, the MRI with a special focus on the rostral brainstem substantiated our neurological assessment and showed a discrete lesion in the right dorsolateral portion of the upper pontine tegmentum. Other less distinctive lesions in the pons and cerebellum were seen on MRI, but no relevant neurological abnormalities were detected. Simultaneous involvement of the spinal cord was excluded by neurological and radiological examinations. Although the patient was considered to have possible rhombencephalitis, the question of whether it was caused by a direct virus invasion or parainfectious demyelination remains unclear.

In humans, an association between micturition disturbances and brainstem involve-

ment has been suspected on pathological and radiological bases.^{3,4} Early in 1926, Holman⁴ documented a relation between micturition disturbance and posterior fossa tumours. Later, a pathological study of brain tumours disclosed a high frequency (63%; 50/79) of voiding difficulties and urinary retention with pontine and fourth ventricle tumours.³ Histological abnormalities were concentrated in the tegmentum of the rostral pons in all such patients.³ The locus coeruleus and adjacent neural tissue were more often involved than other nuclei or regions of the pons.³ However, because of the extensive involvement of these tumours, no localised lesions were noted.³ One recent study with MRI on brainstem stroke disclosed similar results.⁵ Despite numerous reports on the association between multiple sclerosis and micturition disturbances, MRI studies to date have not delineated brainstem lesions specific to the impaired micturition.

In experimental studies, by contrast, Barrington had suggested that in the cat the micturition region was located in the dorsal part of the pontine tegmentum.¹ Recent investigators have reported that it can be located more precisely, in the nucleus locus coeruleus, locus coeruleus alpha, or the dorsomedial part of the dorsolateral pontine tegmentum.² Neurons in the pontine micturition centre may activate the parasympathetic excitatory outflow to the urinary bladder (detrusor), while there also exists a pontine storage centre ventral or lateral to the pontine micturition centre that controls external urethral sphincter function.² Because our patient had atonic bladder and urinary retention, the pontine micturition centre may have been the main site of brain involvement. Atonic bladder may reflect a "shock" state, as has been documented in some stroke patients. However, Sakakibara *et al*⁶ described three patients with atonic cystometrogram 3 months, 6 months, and 3 years after brain-



Brain MRI of the patient. (A) Axial view (2500/103; repetition time/echo time). (B) Sagittal view (2350/103). (C) Coronal view (2920/90). T2 weighted images show a hyperintense focus in the right dorsolateral tegmentum of the rostral pons, just dorsal to the internal edge of the superior cerebellar peduncle including the pontine reticular nucleus, medial parabrachial nucleus, and locus coeruleus. Arrows indicate amorphous lesions in the pons (C). A similar amorphous lesion in the midbrain tegmentum was not confirmed by the axial and sagittal views and is most likely influenced by the cerebral aqueduct (C).

stem stroke, suggesting a prolonged atonic curve as a supranuclear type of parasympathetic pelvic nerve dysfunction.

Griffiths *et al* reported bilateral lesions of the pontine micturition centre leading to a period of urinary retention lasting from 2 to 9 weeks, whereas lesions located on only one side had no obvious specific effect on lower urinary tract function.² This may be accounted for by bilateral innervation of the spinal parasympathetic nucleus by the pontine micturition centre.² However, histology verified that only 15% of the right pontine micturition centre was destroyed.² A recent PET imaging study disclosed that cortical and pontine micturition sites in humans are predominantly on the right side.⁶ It is therefore possible that extensive involvement of a unilateral pontine micturition centre, especially the right side, may cause transient urinary retention as found in our patient. Another possibility is that the amorphous lesions in the pons could have interrupted outflow pathways from the opposite pontine micturition centre.

ATSUSHI KOMIYAMA

Department of Neurology, Urafune Hospital of
Yokohama City University, Yokohama, Japan

AKIHIKO KUBOTA

Department of Neurology, Yokohama City University
School of Medicine, Yokohama, Japan

HIDEO HIDAI

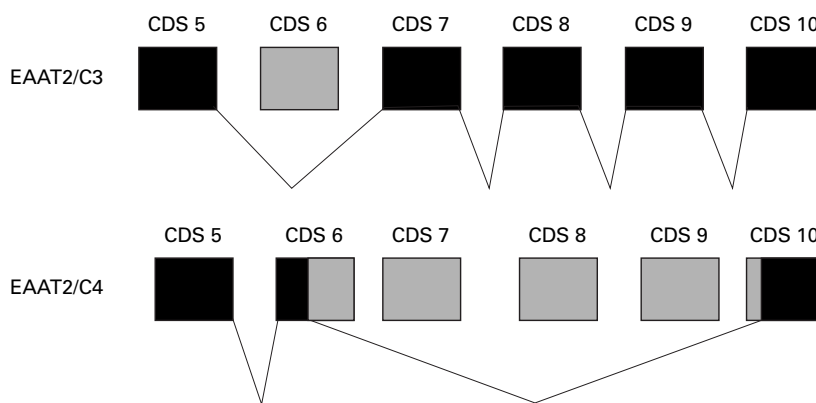
Yokohama Dai-ichi Hospital, Yokohama, Japan

Correspondence to: Dr Atsushi Komiyama; Department of Neurology, Hiratsuka Kyousai Hospital, 9-11 Oiwake, Hiratsuka 254-0047, Japan. Telephone 0081 463 32 1950; fax: 0081 463 31 1865.

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Splicing of the glutamate transporter EAAT2: a candidate gene of amyotrophic lateral sclerosis

Defective glutamatergic neurotransmission may have a critical role in the pathogenesis of amyotrophic lateral sclerosis (ALS). A reduced synaptic glutamate reuptake has been found in the motor cortex and spinal cord of patients with sporadic ALS.¹ More recently, a selective loss of the glial glutamate transporter protein EAAT2 has been described.² Most recently aberrant splicing of the EAAT2 transcript was reported to be the cause for a reduced expression of the EAAT2 protein.³ Several novel EAAT2 transcripts were cloned from patients with ALS and described as disease specific. In vitro expression studies suggested that proteins translated from these transcripts were rapidly degraded and show a dominant negative effect on normal EAAT2 protein which appears to be the predominant glutamate transporter in the CNS.³ A loss of EAAT2



Schematic presentation of alternative splicing in EAAT2 and its relation to the protein coding exons of the human EAAT2 gene.⁵ Alternatively spliced exon sequences are shown in grey. Exon and intron lengths are not to scale. CDS=coding sequence.

can lead to neuronal degeneration through abnormal accumulation of the potential neurotoxin glutamate and excitotoxic mechanisms. This pathogenetic concept was supported by the clinical efficacy of antilutamate drugs in patients with ALS and transgenic models. One of the reported transcripts was characterised by the skipping of the protein coding exon 8 of the EAAT2 gene. This transcript was amplified by polymerase chain reaction from ALS-CSF and suggested as a diagnostic tool in ALS.³ Interestingly, this transcript is identical to an alternative splicing product of the EAAT2 transcript which we have recently reported and named EAAT2/C1. This and another splice product, named EAAT2/C2, have been cloned from normal human brain RNA.⁴

Here we report the cloning of two further EAAT2 transcripts, named EAAT2/C3 and EAAT2/C4. Based on the EAAT2 sequence information we designed specific primers for reverse transcription (RT) of the EAAT2-mRNA using control human brain poly-A+ RNA as template (Clontech, Palo Alto). RT and PCR amplification were performed as described before (RT primer: 5' CAGTTACCATAG-GATACGCTGG; PCR primers: 5' GATAGTTGCTGAAGAG-GAGGGG; 5' CATATC-CTTATTT CT-CACGTTTCC).⁴ PCR cloning and DNA sequencing disclosed two novel EAAT2 transcripts which resulted from splicing of protein coding sequences. EAAT2/C3 originated from a deletion of 234 nucleotides (891-1124; GenBank U03505) corresponding to exon 6 of the EAAT2 gene which is coding for 78 amino acids in the central part of the putative EAAT2 polypeptide (figure).⁵ The EAAT2/C4 transcript was characterised by the deletion of 702 nucleotides ranging from position 992 to 1693 (GenBank U03505). The splicing occurred at internal 5'- and 3'-splice sites which showed an incomplete consensus sequence. EAAT2/C4 resulted from deletion of exons seven to nine and parts of exons six and 10 (figure) with the downstream sequence still in frame.⁵ At the putative protein level EAAT2/C4 showed a loss of 234 amino acids located in the middle and C-terminal part of the polypeptide.

Our findings contribute to the notion that the EAAT2 transcript is highly variable. Splicing of the EAAT2 transcript is also found under normal conditions and may be part of post-transcriptional EAAT2 gene regulation. Furthermore, alternative EAAT2 transcripts were identified in other species. We conclude that splicing of the EAAT2 transcript is unlikely to be ALS specific. The

EAAT2 gene regulation and its pathogenetic relevance are far from completely understood. The use of EAAT2 splicing products as diagnostic tools in ALS would be extremely valuable, but further evidence is necessary before concluding that these splice variants are specifically associated with ALS. However, the evolving knowledge on EAAT2 gene regulation will provide the basis for a comprehensive association study of EAAT2 splicing products in ALS and other neurodegenerative diseases.

THOMAS MEYER

CHRISTOPH MÜNCH

STEFAN LIEBAU

ANDREA FROMM

BIRGIT SCHWALENSTÖCKER

HELGE VÖLKEL

ALBERT C LUDOLPH

Department of Neurology, University of Ulm, Germany

Correspondence to: Dr Thomas Meyer, Department of Neurology, University of Ulm, Albert-Einstein-Allee 11/O25-5, 89081 Ulm, Germany. Telephone 0049 731 177 1200; fax 0049 731 177 1202.

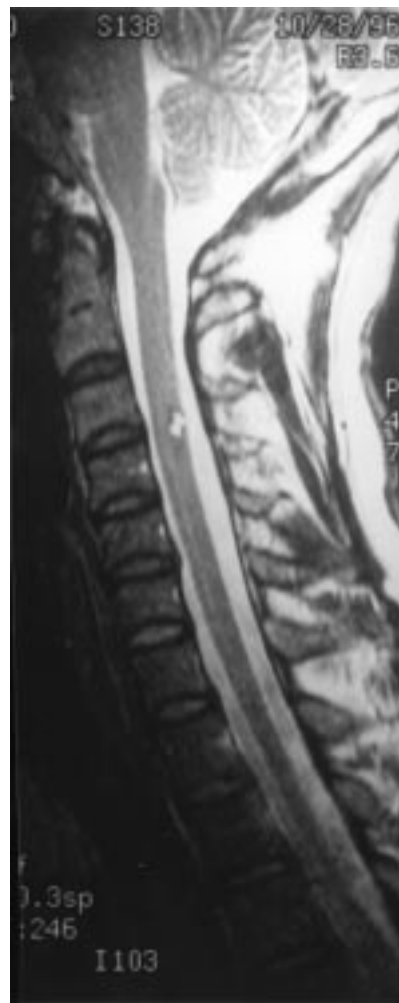
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Lhermitte's sign in cavernous angioma of the cervical spinal cord

The sudden feeling of "painless but unpleasant electric shock-like discharges" originating in the neck or upper back and spreading down the spine into the limbs on flexion of the head was first described in 1917 by Marie and Chatelin and later by Lhermitte in his seminal paper of 1924.¹ It is not a specific symptom but is most commonly encountered in cervical spinal cord demyelination caused by multiple sclerosis.^{2,3} The sign has been found in many other conditions that cause a traumatic or compressive cervical myelopa-

thy, such as cervical spondylosis and epidural, subdural, and intraparenchymatous tumours. It has also been reported infrequently in radiation myelitis, pernicious anaemia (subacute combined degeneration), pyridoxine toxicity, nitrous oxide misuse, cisplatin and docetaxel neuropathies, cervical herpes zoster myelitis, paroxetine withdrawal, Behçet's disease, and systemic lupus erythematosus. Vascular disease of the cervical spine or intraspinal cord has never been noted to produce Lhermitte's sign.

A 48 year old left handed man presented with a history of a "burst, very brief electrical tingling" in the left forearm, hand, and lower leg for almost 2 years. The symptom occurred only on flexion of the neck and abated even when the neck was kept flexed. No other neck movements caused this symptom. A year later, the patient noted mild dysaesthesia in the left arm and leg. A sagittal heavily T2 weighted fast spin echo MR image of the cervical spine showed a small ovoid area of T2 hyperintensity within the posterior cervical spinal cord at the cervical 3–4 level with minimal mass effect. Subtle low signal intensity about its rim suggested hemosiderin deposition (figure). A few weeks later, after raking his yard, the patient experienced acute



Sagittal T2 weighted MRI (TR 3800/TE 96 ms) of the cervical spine shows a small ovoid area of T2 hyperintensity within the posterior cervical spinal cord at the cervical 3–4 level with minimal mass effect. Subtle low signal intensity about its rim suggests hemosiderin deposition.

neck pain. A day later, he noticed diminished coordination of the left arm and leg. A sagittal T2 weighted fast spin echo MRI of the cervical spine obtained a few days later showed an extensive intramedullary low signal intensity area in the midposterior spinal cord compatible with interval haemorrhage, spinal cord expansion, and oedema. Results of spinal angiography were normal. The pain resolved in 10 days, and only mild numbness in the left hand and to lesser degree in the foot persisted. At operation, the lesion was found to be a cavernous angioma. After resection of the malformation, sensory deficits in the left hand and foot worsened, and discomfort with an unpleasant sensation of swelling developed in the hand. For 1 month after the operation, the patient also complained of spontaneous "electrical bursts" in the right arm and both legs. Neurological examination 6 months after the operation disclosed mild weakness of the left arm and hand with diminished stretch reflexes and equivocal plantar response in the left foot. Abnormalities elicited in the sensory examination were decreased pain sensation in the left hand, mild attenuation of two point discrimination, and dysgraphaesthesia in the left fingertips. Mild sensory ataxia on finger to nose testing and mild pseudoathetotic movements of the left hand were also noted.

Lhermitte's sign is a common symptom in neurological practice. However, the pathophysiology of the sign is not well known. Because flexion of the neck causes the dysaesthetic symptoms, it has been suggested that an increased mechanical sensitivity of these damaged myelinated axons causes an abnormal origin or transmission of sensory information. In the cat model, deformation of experimentally demyelinated dorsal columns by <1 mm increased the frequency of action potentials in both spontaneously active and previously silent fibres.⁴ Routine flexion of the neck can lengthen and deform the cervical cord slightly and provide synchronisation of a volley of aberrant activity in damaged dorsal column myelinated axons. Nordin *et al*⁵ reported activation of multiple units in the neurogram of the median nerve, presumably arising from activated sensory fibres in the dorsal columns of a patient with Lhermitte's sign on flexion of the neck. As expected, multiple sclerosis is the most common cause of Lhermitte's sign, occurring in about one third of patients.² The sign, however, is not specific and may be present in other clinical conditions that compress or damage myelinated sensory axons of the dorsal columns of the cervical cord. Occasionally, Lhermitte's sign is the presenting complaint of the underlying medical cause.

To our knowledge, this is the first reported case of Lhermitte's sign caused by a vascular disease in the cervical spinal cord. It was, in fact, the presenting symptom in our patient. The pathological findings confirmed the MRI diagnosis as a cavernous angioma. It is probable that the underlying lesion acted by producing compression or ischaemia on the dorsal columns of the cervical spinal cord.

D KEVIN MURPHY
JOSÉ A GUTRECHT

Department of Neurology, Lahey Clinic Medical Center, Burlington, Massachusetts

Correspondence to: José A. Gutrecht, MD, Department of Neurology, Lahey Clinic Medical Center, 41 Mall Road, Burlington, MA 01805, USA. Telephone 781 744 8631; fax 781 744 5243.

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Autosomal dominant paroxysmal kinesigenic choreoathetosis: a clinical and genetic study of two families

Paroxysmal kinesigenic choreoathetosis (PKC), characterised by brief attacks of abnormal involuntary movements induced by sudden voluntary movements, is either idiopathic (familial or sporadic) or symptomatic. A total of about 20 families with PKC have been reported, with autosomal dominant inheritance in most of them. No genetic study has been reported in familial PKC up to now.

We report two unrelated families with autosomal dominant PKC, in which we performed linkage analyses with loci involved in other paroxysmal movement disorders: (1) the locus for paroxysmal dystonic choreoathetosis (PDC), also known as paroxysmal nonkinesigenic dyskinesia, on chromosome 2q33–35,¹ (2) the locus for AD paroxysmal choreoathetosis/spasticity (CSE), classified as "complicated" PDC, on chromosome 1p,² and (3) the locus for episodic ataxia/myokymia (EA-1) on chromosome 12p13.³

Family A was Portuguese and family B was French. They contained a total of 10 affected and nine unaffected family members, who were all interviewed and examined by the same physician. There was no family history of epilepsy. In one family, three of the five affected members also had migraine with visual aura. Except for one patient, who had had a parkinsonian resting tremor since the age of 52, neurological examination was normal. The phenotypes of the 10 patients were very homogeneous. Age at onset of PKC attacks ranged from 1.5 to 13 years (median 6.5 years). Attacks occurred five to 20 times daily in nine patients and once a year in the other. Attacks were always triggered by a sudden movement of a lower limb (rising from a sitting position, running) that often occurred in response to an unexpected stimulus after sustained immobility. Embarrassment and stress were precipitating factors. In a few patients, fatigue, cold, or menstruation also favoured attacks. The latency between the triggering factor and dyskinesia was 0–2 seconds. Dyskinesias were usually preceded by a short aura (paraesthesias, n=4; muscular tension, n=5) in the affected hemibody. Duration of attacks was 3 to 40 seconds. Involuntary movements involved one side of the body, but sometimes extended rapidly to the whole body, with preservation of consciousness. During attacks, the intensity of the dyskinesias increased and decreased progressively. In addition to frequent dysarthria (n=7) related to orofacial dyskinesia, breathing problems (n=1) and falls (n=5) sometimes occurred during violent

Pairwise linkage analyses with markers from candidate regions on chromosomes 1p, 2q33-35, and 12p13 in two PKC families

Marker	Family	Lod score at $\theta =$						
		0.00	0.01	0.05	0.10	0.20	0.30	0.40
D1S197	A	—	-2.51	-1.16	-0.63	-0.18	-0.01	0.04
	B	—	-6.50	-3.72	-2.54	-1.39	-0.74	-0.31
D2S173	A	—	-4.50	-2.44	-1.59	-0.79	-0.37	-0.13
	B	—	-0.81	-0.18	0.03	0.14	0.13	0.08
D2S163	A	—	-4.50	-2.44	-1.59	-0.79	-0.37	-0.13
	B	—	-1.11	-0.44	-0.19	0.01	0.07	0.06
D2S377	A	—	-4.50	-2.44	-1.59	-0.79	-0.37	-0.13
	B	0.30	0.29	0.26	0.21	0.13	0.06	0.02
D2S126	A	—	-4.50	-2.44	-1.59	-0.79	-0.37	-0.13
	B	—	-2.81	-1.46	-0.93	-0.46	-0.23	-0.1
D12S77	A	—	-4.50	-2.44	-1.59	-0.79	-0.37	-0.13
	B	—	-4.80	-2.72	-1.84	-0.99	-0.52	-0.21
D12S99	A	—	-2.51	-1.16	-0.63	-0.18	-0.01	0.04
	B	—	-6.50	-3.72	-2.54	-1.39	-0.74	-0.31

attacks. One patient wore a helmet during early childhood because of frequent falls. Four out of 10 patients were treated with very low doses of carbamazepine (50–200 mg/day), which completely suppressed the attacks. In six patients who were not treated, however, the frequency of the attacks decreased progressively with age, usually between the ages of 18 and 30, and completely disappeared in five of them between the ages of 11 and 37. Three attacks (lasting 5–20 seconds) were recorded by video-EEG in one patient after carbamazepine withdrawal. No EEG abnormalities were found. Neuroimaging, performed in only four patients (two brain CT and two MRI), was normal.

Because of clinical similarities between PKC and some other paroxysmal movement disorders, we hypothesised that PKC may be allelic to them. Indeed, PDC is also characterised by attacks of mixed involuntary movements (dystonic, and often choreoathetotic), that typically begin as hemidystonia but progressively affect all limbs, trunk, and neck muscles, as well as speech, with preservation of consciousness. Attacks are often preceded by an aura and their frequency decreases with age. However, by contrast with PKC, PDC attacks occur at rest, are precipitated by caffeine and alcohol, not by sudden movements, and last for minutes to hours. In CSE, attacks are similar to those in PDC, except that physical exercise is a precipitating factor, and that some patients exhibit constant spastic paraplegia.² Finally, although EA-1 consists of continuous myokymia and attacks of generalised ataxia, often prevented by acetazolamide, some features are shared with PKC—namely, the frequent kinesigenic origin of the attacks, the presence of a sensory aura, the short duration of the attacks (several seconds to 5 minutes), and the early onset.⁴ Moreover, an EA-1 family in which attacks of kinesigenic episodic ataxia and PKC occurred separately in some members, and jointly in one, has been reported.⁴

After isolation of DNA from peripheral blood, a series of microsatellite markers were typed on: (1) chromosome 2q (D2S164)–2cM–D2S173–2cM–D2S163–2cM–D2S377–1cM–D2S126 (the PDC locus is contained in a 7 cM region flanked by D2S164 and D2S126)¹; (2) chromosome 1p, with D1S197 (the CSE locus is situated in the 2 cM interval between D1S443 and D1S197)²; (3) chromosome 12p, with the 2 markers (D12S372)–4cM–D12S99–1cM–(D12S93)–7cM–D12S77 (the EA-1 locus maps to the 5 cM interval between D12S372 and D12S93).³ Inheritance of PKC was dominant in both families, with two male to male transmissions in one family,

excluding X linked and mitochondrial transmission. There were no asymptomatic obligate gene carriers, suggesting complete penetrance. We assumed autosomal dominant inheritance with a gene frequency of 0.0002 and complete clinical penetrance by the age of 17 years. Allele frequencies for a white population were determined according to the genome database. Two point and multipoint lod scores were calculated using the MLINK program of the Fastlink package.⁵

Results of the two point linkage analysis in both families are shown in the table. All markers tested generated negative lod scores at $\theta=0.00$ except for marker D2S377 in family B. Lod scores below the threshold of -2 were obtained for all candidate regions except for the PDC locus in family B. Multipoint linkage analyses excluded the following intervals including candidate loci in families A and B respectively: 26.5 and 25 cM on chromosome 2q including the PDC locus; 26.5 and 30 cM on chromosome 12p, including the interval containing the voltage dependent potassium channel (KCNAl) gene responsible for EA-1. In conclusion, despite some clinical similarities, AD PKC is genetically distinct from both forms of PDC and from EA-1.

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F PICARD

Department of Neurology, Geneva University Hospital, Switzerland

J TASSIN

M VIDAILHET

INSERM U 289, Hôpital de la Salpêtrière, Paris,

France

Hôpital Saint-Antoine, Paris, France

C MARESCAUX

F PICARD

INSERM U 398, Department of Neurology,

Strasbourg, France

Y AGID

A BRICE

INSERM U 289, Hôpital de la Salpêtrière, Paris,

France

Correspondence to: Alexis Brice, INSERM U 289, Hôpital de la Salpêtrière, Bâtiment de la Pharmacie, 47 bld de l'Hôpital, 75013 Paris, France. Telephone 0033 1 42 16 21 82; fax 0033 1 44 24 36 58.

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Granulomatous angiitis of the CNS causing spontaneous intracerebral haemorrhage: the importance of leptomeningeal biopsy

Granulomatous angiitis (GANS) of the CNS is a rare, idiopathic vasculitis confined largely to the small blood vessels of the CNS. It has also been referred to as “isolated”,¹ “primary”, and “idiopathic”² angiitis of the nervous system. Clinical manifestations are usually the result of multifocal ischaemia and infarction and patients with GANS typically present with a chronic and relapsing but ultimately progressive encephalopathy, characterised by cognitive impairment and multifocal deficits. Less commonly, haemorrhage can occur as a result of infarction, focal necrosis of a vessel wall, or aneurysm rupture and the presentation may therefore be primarily neurosurgical.^{3,4} It is important to recognise this condition because long term clinical remission is possible with immunotherapy. In this letter we present a case which serves as a reminder to neurosurgeons to include GANS in the differential diagnosis of spontaneous intracerebral haemorrhage and emphasises the importance of leptomeningeal biopsy.

A forty six year old woman was admitted to our unit with a 24 hour history of confusion, vomiting, dysphasia, and a generalised seizure. The patient also had a 30 month history of deteriorating work performance and had had episodes of nausea, vertigo, and headache lasting 1 to 2 days. After one of these episodes she was investigated by one of us (SM). Neurological examination and a CT were normal. Diagnoses of migraine and Ménière's disease were considered. Four months before admission, she had experienced transient mild dysphasia and left hemianaesthesia.

On admission to our unit, she was drowsy but opened her eyes to voice and obeyed simple commands. She had a left retinal haemorrhage and an expressive dysphasia. She was afebrile, there was no meningism, and general examination was normal. Brain CT showed an extensive area of low density involving both grey and white matter of the left frontal lobe, with three separate areas of intraparenchymal haemorrhage and mild mass effect. She was started on dexamethasone, phenytoin, and acyclovir and arrangements were made for MRI and MR angiography to be performed the following day.

An improvement was noted overnight, but the next day her clinical condition deteriorated. Urgent CT was performed and this showed further haemorrhage into the left frontal lobe with appreciable midline shift (figure). Immediately after the scan her left pupil became fixed and dilated. An urgent left frontal lobectomy was performed.



Brain CT after clinical deterioration. There is extensive patchy haemorrhage into the left frontal lobe with marked mass effect.

Macroscopically the left frontal lobe was swollen, with multiple small areas of haemorrhage in the cortex and white matter, and thrombosis of superficial cortical veins. Histological examination disclosed a coexistent pattern of granulomatous and necrotising non-granulomatous vasculitis affecting the small leptomeningeal and intracerebral blood vessels. Occasional leptomeningeal vessels were occluded by thrombus. The granulomatous lesions featured an infiltrate of lymphocytes and histocytes within blood vessel walls. The vascular intima was variably thickened by a fibrocellular proliferation and small numbers of Langhans and foreign body type giant cells were scattered individually within the media of some vessels. The leptomeninges contained a dense infiltrate of mononuclear inflammatory cells. The cerebral tissues were oedematous with extensive extravasation of erythrocytes and diffuse hypoxic neuronal changes but there was no evidence of a discrete area of infarction. Special stains for organisms (zinc, gram, PAS, PAS-D, Giemsa and GMS) were negative. Viral inclusions were not seen.

Haematological investigation disclosed a mild neutrophil leucocytosis, but haemoglobin, platelet count, and erythrocyte sedimentation rate were all in the normal range as were serological investigations including C reactive protein, complement assays, antinuclear antibodies, double and single stranded DNA antibodies, and rheumatoid antibodies.

The patient was treated intensively with a combination of oral cyclophosphamide and intravenous methyl prednisolone for one week followed by oral cyclophosphamide and prednisone. Treatment was complicated by haemorrhagic cystitis (for which oral cyclophosphamide was changed to pulsed intravenous cyclophosphamide), and organic psychosis. At 2 years the patient is clinically stable. Immunotherapy is being gradually reduced. She has a fixed frontal lobe deficit consisting of impulsivity, a loss of control of emotions, reduced verbal fluency, and impaired insight. Serial CT and MRI show only postsurgical change in the left frontal lobe.

The importance of this case is firstly that it draws attention to the protean manifestations of this rare but treatable condition. Other reported presentations include recurrent intracerebral haemorrhage, radiculomyelopathy, cerebral and spinal aneurysms, subarachnoid haemorrhage, seizures, and mass lesions.^{1,2,5}

Secondly, this case emphasises the fact that the disease mostly affects small vessels of the leptomeninges. Neurosurgeons are most likely to encounter this disease in the setting of a request by their neurology colleagues for a diagnostic brain biopsy. Moore suggested that the ideal biopsy in these patients is a 1 cm wedge of cortex including leptomeninges and preferably containing a cortical vessel.¹

Our patient ultimately required urgent decompressive frontal lobectomy. The diagnosis of GANS was not suspected preoperatively and the inclusion of leptomeninges in the surgical specimen was fortuitous. We would advise others undertaking the evacuation of an intracerebral haematoma of uncertain aetiology to obtain a leptomeningeal biopsy at the same time, particularly when there is a background of neurological symptoms.

Other investigations may not be helpful. Brain CT and MRI are abnormal in 30%-65% and 75%-100% of cases respectively and may show a wide variety of lesions. Angiographic abnormalities are present in 50%-90% of cases but are not specific for GANS. The CSF may be normal.^{1,2} It is essential to differentiate GANS, from the many secondary causes of cerebral vasculitis such as giant cell arteritis. The presence of markers of systemic, inflammatory, or autoimmune disease should suggest an alternative diagnosis.

Because GANS is rare, our knowledge of its natural history and optimum management is incomplete. Early reported cases of GANS were invariably fatal¹ but immunotherapy has now been shown to improve symptoms and result in sustained remission in some cases. The results with corticosteroids alone have been disappointing and the combination of prednisone with cyclophosphamide is the mainstay of treatment.^{1,3,5}

MARTIN HUNN

SIMON ROBINSON

Department of Neurosurgery

LEN WAKEFIELD

Department of Pathology

STUART MOSSMAN

DAVID ABERNETHY

Department of Neurology, Wellington Hospital, Wellington, New Zealand

Correspondence to: Mr Martin Hunn, Neurosurgical Unit, Wellington Hospital, Capital Coast Health Ltd, Private Bag 7902, Wellington South, New Zealand.

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Intravesical atropine suppression of detrusor hyperreflexia in multiple sclerosis

Multiple sclerosis commonly causes urinary frequency, urgency, and urge incontinence resulting from detrusor hyperreflexia. This

might be associated with voiding difficulties due to detrusor sphincter dyssynergia. These symptoms can be treated effectively with antimuscarinic drugs (principally oxybutynin) and clean intermittent catheterisation, but the antimuscarinic side effects limit clinical usefulness. Typically these are dry mouth and blurred vision, but include constipation, reflux oesophagitis, and flushing.

Oxybutynin, formulated for intravesical administration, has been reported to be effective for suppressing detrusor hyperreflexia with low incidence of side effects in various neuropathic disorders.^{1,2} However, this preparation is not widely available.

Atropine is a cheaper, easily obtainable, antimuscarinic drug. Administered intravesically it has been shown to be effective in increasing bladder capacities without side effects in patients with spinal cord injury.³ However, the only study was small and uncontrolled. Whereas the pathologies of multiple sclerosis and spinal cord injury are different, the bladder impairments are similar. This study was designed to investigate the efficacy of intravesical atropine in increasing bladder capacities in patients with multiple sclerosis with detrusor hyperreflexia.

The study received ethics committee approval. Written informed consent was obtained from each patient.

Patients with a definite diagnoses of multiple sclerosis and urodynamically demonstrated detrusor hyperreflexia were recruited into the study. Each was taking oral antimuscarinic medication and using clean intermittent catheterisation. A sample size calculation based on previous data³ identified a target recruitment of 15 patients to achieve a significance level of 0.05 with a power of 0.80 using a crossover study design. Eighteen patients were contacted, of whom 16 consented and 15 completed the study.

Antimuscarinic drugs were stopped 2 days before cystometric testing. Patients attended on two occasions. They were allocated 30 ml of either atropine (6 mg) in normal saline or normal saline only (as placebo). This was done according to random code with both patient and investigator blinded. An independent nurse prepared the solutions.

Standard static saline fill cystometry with a filling rate of 50 ml/min was performed before and 2 hours after intravesical instillation of the test preparations. As this was a first randomised study of a single dose of intravesical drug the outcome measure used was cystometric bladder capacity and not urgency or episodes of urge incontinence. A single prophylactic dose of ciprofloxacin (250 mg) was administered orally on each occasion. At the beginning and end of each cystometric study the patient's heart rate and blood pressure were measured. All patients were questioned about known antimuscarinic side effects. Blood samples were collected for atropine assays 2 hours after instillation of the test solutions.

Urodynamic data were not normally distributed, therefore non-parametric analysis techniques were used. When comparisons between the difference in change in cystometric bladder capacities were made a Wilcoxon sign ranked test was used quoting the 95% Wilcoxon confidence interval.

The study group consisted of 15 patients (six men and nine women) with a median age of 51 years (range 39-73 years). All patients retained their test solutions after each instillation. The results are shown in table 1. After atropine the bladder volumes increased by a

Cystometric bladder capacities (CBC) for atropine and placebo (saline)

	CBC (ml) (95% CI)	Change in CBC (ml) (Wilcoxon 95% CI)
Atropine		
Pretreatment	183 (144.5-302.5)	
Post-treatment	350 (195.3-451.3)	93 (45 to 170)
Saline		
Pretreatment	180 (124.6-312.8)	
Post-treatment	159 (143.7-331.8)	-2.5 (-21.5 to 14.5)

median value of 93 ml (95% confidence interval 45.0-170 ($p=0.001$)). After saline the cystometric bladder capacity did not change significantly.

No significant changes were found in blood pressures or pulse rates. No side effects were reported by any patient. Atropine was not detected in blood samples 2 hours after intravesical instillation (limit of detection 0.05 mg/l).

This early study provides evidence in favour of the efficacy of intravesical atropine in increasing the cystometric bladder capacity in patients with multiple sclerosis. Cystometric bladder capacity was chosen as an outcome measure because it has been shown to be sensitive to the influence of orally administered antimuscarinic drugs used for the treatment of detrusor hyperreflexia in multiple sclerosis.⁴ It is therefore likely that urgency and urge incontinence will be improved with the administration of intravesical atropine. However, this will require testing in a randomised controlled therapeutic trial.

The patients did not identify any side effects during the 2 hours after the administration of the atropine. It has been shown that orally administered oxybutynin will induce antimuscarinic side effects in a similar period.⁵

The absence of measurable drug in the blood at the time of the clinical effect is encouraging. The results show promise and if clinical efficacy were demonstrated this approach would be a useful addition to the therapeutic options for urinary incontinence in multiple sclerosis.

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CARL DEANEY

Academic Department of Surgery, Imperial College School of Medicine, Charing Cross Hospital, London W6 8RF, UK

SCOTT GLICKMAN

Department of Medical Rehabilitation, Imperial College School of Medicine, Charing Cross Hospital, London W6 8RF, UK

TIMOTHY GLUCK

Medicine for the Elderly, Barnet General Hospital, Wellhouse Lane, Barnet, Herts, EN5 3Df, UK

JAMES G MALONE-LEE

Correspondence to: Professor James G Malone-Lee, Department of Geriatric Medicine, University College London Medical School, St Pancras Hospital, 4 St Pancras Way, London NW1 0PE, UK.

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Prothrombotic mutations and ischaemic stroke at a young age in two sisters

We examined two sisters who had an ischaemic stroke at 32 and 41 years respectively. One had the prothrombin 20210 G to A variant¹ and mild hyperhomocysteinaemia. The other had two prothrombotic mutations: the factor V Leiden mutation² and the prothrombin 20210 G to A variant.¹ We argue that these abnormalities may have caused the strokes.

Patient III-36 (pedigree, figure) was admitted at the age of 41 years with a left sided paresis. Her medical history was unremarkable, including the absence of migraine. Neurological examination showed a mild left sided paresis. Blood pressure was normal. She had no livedo reticularis. Brain CT showed a right sided cerebral infarct. Cardiological investigation, carotid angiography, and laboratory testing were normal, including investigation of antiphospholipid antibodies, lipid profile, fasting and post-methionine loading homocysteine concentrations, antithrombin III, protein C, and protein S. The patient was treated with aspirin and did not have arterial ischaemic disease (or venous thrombosis) until now. Resistance to activated protein C (APC) was measured as described² and the n-APC-SR was 0.66 (normal >0.84). As expected from this value, the patient was found to be a carrier of the factor V Leiden mutation.² Subsequently, she was also shown to be a carrier of the prothrombin 20210 G to A variant.¹

Patient III-37 was admitted at the age of 33 years because of an acute left sided paresis. One year before, she had experienced a transient weakness of the right leg. Otherwise, her medical history was unremarkable (no migraine). She smoked 20 cigarettes a day, did not drink alcohol, and did not take oral contraceptives. She had a left facial palsy, hemianopia, and hemiparesis. Blood pressure was normal. She had no livedo reticularis. Brain CT showed an old left frontoparietal infarct and a recent right frontoparietal infarct. Laboratory investigation, including lipid profile, protein C, protein S, and antithrombin III, cardiological investigation, and carotid angiography were normal. Fasting homocysteine concentration was raised (28.2 $\mu\text{mol/l}$), without abnormal post-methionine loading concentration. She was treated with aspirin, folate, and pyridoxin and did not have arterial or venous thrombosis until now. APC resistance was normal (n-APC-SR of 1.09), and the factor V Leiden mutation was not present. She was a

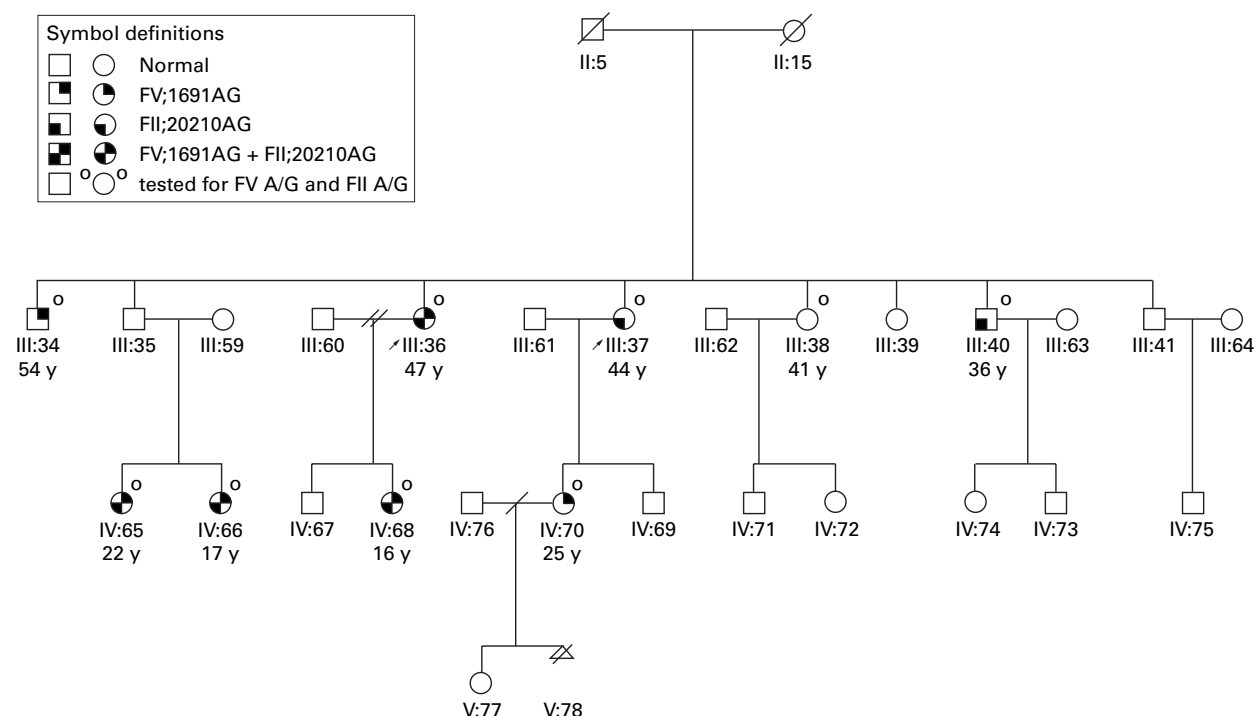
carrier of the prothrombin 20210 G to A variant.

After informed consent, we prospectively investigated the family members of the probands. DNA testing was not performed in all family members (see pedigree). Medical history of all family members was unremarkable (no ischaemic heart disease, stroke, migraine, or deep venous thrombosis), except for III-39 who had mental retardation, epilepsy, and blindness (she could not be studied). The factor V Leiden and prothrombin variant were investigated in III-34, III-38, III-40, IV-65, IV-66, IV-68, and IV-70. The factor V Leiden mutation was present in III-34 and IV-70, the prothrombin variant in III-40, both variants in IV-65, IV-66, and IV-68, and no mutation in III-38. III-35 (who was not tested) may have both mutations, because her two daughters carry both mutations. III-61 (who is not a relative) probably carries the factor V Leiden mutation, as his wife has the prothrombin mutation, but their daughter has the factor V Leiden mutation. Fasting and post-methionine loading serum homocysteine concentrations were normal in III-34, III-38, III-40, III-41, IV-65, and IV-70.

The occurrence of a stroke in a young person is relatively rare. It is even more rare when two first degree relatives have a stroke at a young age. The second situation strongly suggests a genetic cause, which reduces the list of possible causes considerably.³ On clinical and radiological grounds and after laboratory and cardiac investigations, in the probands many hereditary causes of stroke were excluded (mitral valve prolapse, atrial myxomas, cardiomyopathies, CADASIL, Sneddon's syndrome, MELAS, and abnormalities of protein C, protein S, and antithrombin III). In homocystinuria thrombotic events are invariably more severe than in our probands, although the occurrence of mental retardation, epilepsy, and blindness in subject III-39 is compatible with homocystinuria (unfortunately, she could not be studied). III-37 had mild hyperhomocysteinaemia, but it is unlikely that this was the (only) cause for her strokes, as hyperhomocysteinaemia mostly causes premature atherosclerosis, microangiopathy, and leukoencephalopathy, which were not found. We therefore considered the prothrombotic mutations as the most likely cause.

The factor V Leiden mutation occurs in about 4% of the Dutch population,² and the prothrombin mutation in 1% to 2%.¹ The simultaneous occurrence of both mutations in one subject can therefore be calculated as 0.04% to 0.08%—that is, 6000 to 12 000 persons in The Netherlands (about 15 million inhabitants). Nevertheless, so far only one Dutch family in which both mutations occur has been described.¹ All members in this family with both genetic defects experienced venous thromboses.¹ The only other published pedigree in which both mutations occur originates from France.⁴ In this pedigree only one subject carried both mutations, and she had recurrent venous thrombosis, but no arterial ischaemic events.⁴ The risk for venous thrombosis in patients with both mutations is probably high, as it is known that the factor V Leiden mutation enhances the risk for thrombosis in patients with other prothrombotic states, such as protein S and protein C deficiencies.⁵

Although the association of prothrombotic mutations, such as the factor V Leiden mutation and the prothrombin variant, with



Family tree.

(recurrent) venous thrombosis is now well established, the association with arterial thromboembolism is not clear.⁵ Population and case-control studies have shown that the factor V Leiden mutation is not a risk factor for myocardial infarction or cerebrovascular disease.⁵ Nevertheless, this mutation has been associated with ischaemic stroke.⁶ The relation between the more recently discovered prothrombin 20210 A to G mutation¹ and arterial disease has not yet been intensively studied, but seems unlikely.⁶ It is, however, possible that the strokes in the probands can be attributed to the co-occurrence of two risk factors (prothrombin mutation and factor V Leiden mutation in one, and prothrombin mutation and hyperhomocysteinaemia in the other), because it is likely that a synergistic interaction occurs between thrombogenic risk factors. To study this further, a case-control study determining the importance of a combination of thrombogenic risk factors in unselected young patients with stroke is necessary.

J HAAN
G G SCHOONMAN
G M TERWINDT
M D FERRARI
Departments of Neurology

R M BERTINA
Haemostasis and Thrombosis Research Centre,
Leiden University Medical Centre,
The Netherlands

L J KAPPELLE
University Hospital, Utrecht

J HAAN
Rijnland Hospital, Leiderdorp

Correspondence to: Dr J Haan, Department of Neurology, K5Q, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands. Telephone 0031 71262134; fax 0031 71248253.

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- 3 Rastenyte D, Tuomilehto J, Sarti C. Genetics of stroke—a review. *J Neurol Sci* 1998;**153**:132-45.
- 4 Conard J, Mabileau-Brouzes C, Horellou MH, *et al.* Thrombophilie multigenique: anomalie genetique du facteur II et mutation du facteur V Leiden. *Presse Med* 1997;**20**:951-3.
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- 6 Longstreth WT, Rosendaal FR, Siscovick DS, *et al.* Risk of stroke in young women and two thrombotic mutations: factor V Leiden and prothrombin gene variant (G20210A). *Stroke* 1998;**29**:577-80.

BOOK REVIEWS

Neuroimaging and the Psychiatry of Late Life. Edited by DAVID AMES AND EDMOND CHIU. (Pp 242). Published, by Cambridge University Press, Cambridge, 1997. ISBN 0-521 49505 9.

The continuing rapid expansion of neuroradiology, with new technologies and improvements in more well established techniques, have sharpened the tools with which to examine neurological and psychiatric diseases of old age. Investigation of, for example, the MRI findings in vascular dementia and depression, measurements of medial temporal lobe structures in Alzheimer's disease, and functional imaging

studies of schizophrenia, have led to new insights into the diagnosis, prognosis, and symptomatology of these ill understood diseases. However, there are two obstacles in the understanding of this expanding area of research for the interested neurologist and psychiatrist—namely, understanding of the basis of the technology and relating the research findings to best clinical practice. The remit of this text covers both these deficiencies.

For the non-physicist getting to grips with the basic principles and methodologies of neuroimaging can be daunting. The first section of this book explains the basic principles behind the hardware of the imaging department and this is aided by many excellent diagrams. The general clinical indications and safety issues of structural (CT and MRI) and functional (PET, SPECT, and EEG) imaging techniques are well reviewed and illustrated.

The second section of the text explores the research questions and summarises the answers so far in the field of old age psychiatry. Interpretation of imaging research in abnormal elderly patients, with regard to subject selection, imaging technique, and the relation to normal aging, is one of the main dilemmas in this field. This is fully discussed in the admirable chapter on normal aging, which commences this review of the research. Other chapters on Alzheimer's disease, vascular dementia, other dementias, delirium, affective disorders, and schizophrenia of late onset continue this well referenced text. Besides presenting the data for the clinician, this comprehensive review will also be appreciated by researchers in this field.

The third part of this book returns to the application of these results to clinical practice. Both an American and European perspective on the clinical interpretations of the above data are presented and the conclusion can be quoted "Our ability to image the brain, however, has in some cases outpaced

our ability to understand the clinical implications of the structural and functional findings seen using modern imaging techniques". In other words this interesting research which has been so excellently summarised here has yet to make real impact on routine clinical practice.

CLARE GALTON

Progress in Neurological Surgery, Volume 14, Gamma Knife Brain Surgery. Edited by L D Lunsford, D Kondziolka and J C Flickinger. (Pp 228, US\$188.00). Published by Karger, Switzerland 1998. ISBN 3-8055-6637-9.

Stereotactic radiosurgery has been with us for about 30 years. The pioneering work of Lars Leksell was carried out at the Karolinska Institute in Stockholm, but in the United Kingdom, the National Stereotaxic Radiosurgery Unit in Sheffield has now been active since 1985. In theory, indirect methods of treatment for neurosurgical conditions are to be preferred to direct open surgery and it already seems that in a number of areas indirect techniques have already largely replaced surgery as the treatment of choice, for example, in the endovascular coiling for the treatment of intracranial aneurysms where direct surgery seems destined to become a rare event for this condition in the not too distant future. It is therefore disappointing that the application of the stereotaxic technique to radiosurgery has not been more productive in this respect. However, some progress has been made. This review in the series *Progress in Neurological Surgery* sets down the current state of play in this field. The experience recorded in this volume is entirely North American and, as most of the conditions treated by this technique are rare, it would have been valuable to have included the by now quite extensive experience from the Scandinavian and the United Kingdom units. The papers in the volume, as is usual in this type of publication, are of variable quality and of variable value - one wonders at the need for a chapter on the technology and physics of the technique. On balance however it is an interesting volume and there are some useful data on the management of quite rare conditions. This may be particularly useful to the "modern" neurosurgeon who now has to discuss, using appropriate data, the alternatives to surgery with each patient as an integral part of the "informed consent" procedure. The chapters on *Patient outcomes after Arteriovenous and Cavernous Malformations* are potentially useful in this respect. The section on Frontiers of Radiosurgery is more problematic, and because of the small number of cases involved it is very difficult to form any useful conclusions about the place of this treatment technique in the management of these difficult conditions. One question, for example, whether it will ever replace tried and tested surgical techniques in the treatment of disorders such as trigeminal neuralgia or the involuntary movement disorders.

Despite the persuasive data presented in at least some of the chapters in this volume it remains questionable whether the enormous expense of these dedicated machines is really justified in this modern age. We wait with some interest a future volume on the LINAC treatment of a similar spectrum of disorders.

The book is compact and well presented and can certainly be recommended for the departmental library.

DAVID HARDY

Central Pain-A Neurosurgical Challenge. Edited by Carlo Alberto Pagni. (Pp 212, Price not known). Published by Minerva Medica, Italy, 1998. ISBN 88-7711-303-0.

Although recognised for more than 100 years, central pain remains ill-defined, poorly understood, intensely debilitating and, in the majority of patients, refractory to therapy. In this text, Professor Pagni attempts to define, classify, and review critically the multitude of treatments that have been proposed for this most challenging of conditions.

The book begins with a review of the history of the condition and a discussion of its definition, nosology, and clinical spectrum. There follows a survey of the lesions which cause central pain, both spontaneous and iatrogenic, theories about its aetiology, and the various measures available to treat it. There is an extensive bibliography for further reading.

The book provides a critical review of the literature on central pain, interspersed with personal observations from over 30 years of experience in the field. It is written in a succinct style that presents theories and therapies in a historical sequence, followed by the author's comments on current indications and clinical outcomes. If I have one criticism of this book it is the index, which is by subject heading rather than strictly alphabetical sequence, making it cumbersome for cross-referencing. This, however, is a minor irritation.

In summary, this is a thoughtful and enjoyable book. It takes a logical look at a subject which, by its very nature, has a literature containing many anecdotal reports that can be hard to evaluate in isolation.

ROBERT MACFARLANE

Foundations of Neurobiology. Edited by Fred Delcomyn. (Pp 649, £32.95). Published by W H Freeman, Macmillan Distribution, Basingstoke, 1998. ISBN 0-7167-2627-0.

There is nowadays a trend in the training of doctors to integrate basic science with medicine in a bid to make more sense of the biology one learns as a medical student. Furthermore in the long term it is hoped that as a result medical practitioners will seek a more scientific basis to their art, even if the current funding bodies and training schemes are not always especially encouraging in this respect. It is in this context that Delcomyn finds his book on the "*Foundations of Neurobiology*", a book that has clearly come from years of patient teaching and explanation. Indeed the whole emphasis of the book is to teach, as is evidenced by the language used; for example "As you will learn in Chapter 5, the . . ." The book is divided up into six sections, each of which contains up to half a dozen chapters. The sections are conventional in their topics, beginning with the cellular and organisation of the nervous system, followed by sections on the motor, sensory and integratory systems and concluding with a section on

neural plasticity. Each chapter is characterised by clear text, beautiful multicoloured figures and punctuated by short summary paragraphs. In addition scattered throughout each chapter are separate boxed items which detail experimental techniques, typically with a gorgeous illustrative figure. At the conclusion of each chapter are a few key references which gives the enthusiastic student some realistic hope of finding and reading important review articles. Finally at the end of the book, to the relief of all students, is a glossary of terms along with a brief chapter detailing anatomical orientation. However, despite the obvious attraction of this book, the major problem (as its title implies) relates to its concentration on neurobiology at the expense of any neurological application. There is therefore a great deal of discussion on the functional organisation of the nervous system in a number of different species, including invertebrates. This is useful in establishing the principles for the organisation of more complex neural networks as are found in the mammalian nervous system, but in the context of a busy clinical training seems somewhat erudite. Although I found this book profoundly interesting and useful, especially given the complexities of the mammalian nervous system, as well as being well-presented, it does have limited appeal to students. For example, one has to search hard to find the section on movement disorders in the section on motor control and then the account is limited and not put into any major therapeutic context. Similarly the account on cranial nerves is presented somewhat in isolation. Overall the book is a very enjoyable experience, both in terms of the clarity of the text and the visual aesthetics of the figures. However, the recent shift in medical training means that books such as this are increasingly going to struggle to find an audience.

ROGER BARKER

Outcomes in Neurological and Neurosurgical Disorders. Edited by Michael Swash. (Pp 614, £80.00). Published by Cambridge University Press, Cambridge 1998. ISBN 0-52144327-X.

This is a timely moment to publish a book which takes an analytical look at outcomes in the common neurological and neurosurgical procedures' obsessed as we seem to be at present with evidence based medicine. In addition we are rapidly moving towards an era when therapies are becoming available for many neurological diseases, hitherto deemed more suitable for pastoral care, and our understanding of treatment trials and the importance of comparative treatment groups is essential for local and regional health planning. It places the work of neurosciences effectively in context with the rest of medicine and provides a multitude of informative lessons on patient management and our interpretation of medical dogma and established practice.

Before embarking on the more traditional interpretation of current neurological and neurosurgical therapy there are four invaluable chapters in the introduction section. These take a practical view on the aims of studies designed to evaluate and measure outcome as well as their financial impact on the health services in a cost-benefit analysis. Although these subjects may seem a little stodgy to pure clinicians they provided

important background within which to understand the aims of the book and to set up a pattern of interpretation for the clinical sections which followed. By and large the authors keep to the task set out to them in the introduction and the range of subjects covered is broad and includes the traditional subjects of vascular disease, trauma, tumours, degenerative diseases, infections, epilepsy, and coma. In addition the contemporary issues of surgery in movement disorders and rehabilitation were addressed well. However, the quality of a few of the sections was variable and some of the authors appeared to stray from their brief preferring to provide a tired and rather automated version of therapy for a given group of diseases occasionally providing the reader with a *deja vu* phenomenon.

I cannot pretend that this is an essential book for neuroscience libraries, but it does provide important insights for those planning treatment or outcome studies and may also be of value for medicolegal work.

NEIL ROBERTSON

Gene Therapy for Neurological Disorders and Brain Tumours. Edited by E Antonio Chiocca and Xandra O Breakefield. (Pp 458 US\$135). Published by Humana Press, New Jersey, 1998. ISBN 0-89603-507-7.

This book is a brave attempt to discuss the burgeoning field of gene therapy for neurological disorders. To many clinicians, gene therapy has not to date lived up to all the hype and excitement of when it was first suggested. However, as the editors point out in their preface, this has been a little unfair and it remains an exciting area that is worthy not only of intellectual interest but also the possibilities of therapy in the future. The complexities, however, of this technique, cannot be overestimated. Neurons are postmitotic; a brain has a degree of immune privilege by virtue of the blood-brain barrier and other immunological differences to the majority of other organs. The unbelievable complexity of the nervous system makes the "fixing" of any genetic defects incredibly difficult.

The potential uses of gene therapy are not restricted to single gene Mendelian disorders, although it is most likely that this is where the most significant progress will be made. There are more common degenerative diseases, such as Parkinson's disease and Alzheimer's disease, where gene therapy can also be considered. In this instance, it is not necessary to correct an identified genetic defect but rather support the dying cells by transfection with genes in coding growth factors and so forth.

All of these issues are discussed in some depth in this book, the first section dealing with the variety of vectors, in particular different viral systems. This is clearly crucial to the problem. As one can imagine, one will need to select an appropriate vector for the problem in hand. If one wants to fix a genetic defect in neurons, then one will need a vector that can effectively transfer the appropriate gene to the appropriate place in the genome, with the appropriate regulatory factors associated, into non-dividing cells. There are emerging vectors that have many if not all of these properties. However, sometimes it will be important to target dividing cells, particularly in tumour disorders, and therefore another vector system

will be required. There are a number of important issues as to the construct that is transferred by these vectors. Will the whole gene be necessary? How will the gene, once it is incorporated, be regulated?

Most of the book deals with many of these issues and even discusses rat brain models. The much smaller second part deals with some neurological disorders, with chapters on gene therapy, ischaemic stroke, Parkinson's disease, Huntington's disease, pain and lysosomal storage disorders, and gene transfer for CNS regeneration.

This is an interesting book, containing a lot of useful information by some of the world leaders in the field. It sets the scene for potential developments well. However, it quickly moves into the jargon of the field and I think this will limit its accessibility to general neurologists who are not au fait with some of the molecular genetic terminology.

NICK WOOD

Clinical Neurology-Parkinsonism. Edited by N P Quinn. (Pp 225, £30.00). Published by Harcourt Brace and Co, Sidcup, Kent, 1997. ISBN 0-7020-2309-4.

Currently the most exciting new developments in Parkinson's disease relate to the genetics and role of α -synuclein in the pathogenesis of this disorder, and the resurgence of neurosurgery that dominates new management strategies. These areas are therefore well covered in this book which (like others in this series) is a well structured and topical review of, in this case, Parkinsonism. However, unlike previous volumes, abstracts are now provided along with a reference list in which the key articles are highlighted. This is a useful addition as it not only lays out the structure of the chapter, but allows the interested reader to supplement their understanding by the acquisition of a few essential source articles.

The book opens with a chapter on the clinical features of Parkinson's disease (Quinn) which is supplemented later on by chapters on other parkinsonian syndromes, including multiple system atrophy (Quinn and Wenning), progressive supranuclear palsy and corticobasal degeneration (Litvan), as well as other causes of parkinsonism (Tison). These chapters are helpful in defining the characteristic features of these diseases and by so doing the differences between them which should allow for a more accurate clinical diagnosis in life. However, the fact that all these conditions ultimately rely on pathology for diagnosis can create significant discordance between clinical features and disease state, and this is exacerbated by the desire to try and fit an atypical patient into one of these categories. In this respect the discussion on Lewy body dementia is timely, given its increasing recognition as a cause of dementia. The relation of this condition to Parkinson's disease is still far from clear and this is acknowledged by Lennox and Lowe in their chapter on dementia and Lewy bodies.

The book, however, does not stay purely within the realm of clinical phenotypes. Schapira provides a familiar chapter on the pathogenesis of Parkinson's disease and Wood reviews the genetic literature and Ben-Shlomo the epidemiology. These are comprehensive chapters and again highlight the difficulties of conducting such work given our inability to make a definite diagnosis of

Parkinson's disease in life. There is limited discussion on α -synuclein and the recent identification that this forms the major filamentous component of Lewy bodies and Lewy neurites is obviously not mentioned, although it may prove to be the gold standard for diagnosis in the future. Furthermore, the recent identification of a second gene (*parkin*), this time in autosomal recessive juvenile parkinsonism, is also not covered in this book, which highlights the speed with which these books can become out of date.

The chapters on management are useful if not inspiring. Oertel and Quinn discuss the issue of drug therapy well, both in terms of overall aims and specific advice, and LeWitt discusses rather turgidly newer pharmacological therapies. The controversy as to the treatment of young onset Parkinson's disease is touched on in both chapters, although no clear scientifically proved answers are provided. The surgical management is then discussed by Obeso and colleagues, who present data on the newer techniques of pallidotomy, deep brain stimulation, and transplantation. This is a burgeoning area of interest although the basic wiring diagram of the basal ganglia, that regularly turns up in chapters of this sort, is a gross simplification, which may explain some of the limited effects of these surgical manipulations. Since this book came out there is now much more information on the cognitive consequences of pallidotomy, as well as early studies addressing pallidal versus subthalamic stimulation in the treatment of Parkinson's disease. Furthermore the discussion on transplantation in this chapter is not especially critical both in terms of the failure of some centres to follow scientifically proved methods of tissue preparation and implantation as well as adherence to the CAPIT-PD guidelines. This has meant that comparisons between centres with this experimental procedure cannot be done easily, if at all.

Overall the book is very rewarding and is probably more of interest to those not directly working in the field of movement disorders and Parkinson's disease. It is generally clear and concise and combines scientific data with practical advice. It is a shame that there is no discussion of the cognitive and affective aspects of Parkinson's disease, outside the context of Lewy body dementia, but there again one can't have everything!

ROGER BARKER

Ischemic Stroke: from Basic Mechanisms to New Drug Development. Edited by C Y Hsu. (Pp 166, Sw fr 159). Published by S Karger AG, Switzerland, 1998. ISBN 3-8055-6560-7.

This volume in the *Monographs in Clinical Neuroscience* series provides a timely overview of recent advances in stroke therapy. The list of contributors includes many prominent names from current experimental stroke research, and the contents of the book generally live up to the expectations that such a list generates. Aspects of experimental neuroprotection that were covered in individual chapters include glutamate receptor mediated ischaemic neuronal death, oxidant mechanisms, nitric oxide, inflammatory mechanisms, temperature modulation of ischaemic injury, apoptosis, and neurotrophic factors. The chapters vary somewhat in character. For example, the chapters on glutamate neurotoxicity and inflammatory mechanisms

provide an overview of the recent literature, whereas that on oxidant mechanisms provides focuses more on the use of transgenic and knockout animals to study free radical injury in ischaemia. Both types of chapter provide useful information, but the former variety seemed to me to sit better with my perception of the aims of the book.

The second part of the book contains three chapters. The first of these considers the current status of new drug development for stroke, with brief sections on both clinical trials of thrombolytic and neuroprotective therapy. It also contains a useful analysis of how protocols for clinical trials might be advanced, with consideration of clinical outcome assessment, the need for early enrollment, sample size issues, and the utility of surrogate end points. The second of these two chapters focuses on

new MRI techniques in acute stroke. The final chapter provides a useful overview of future directions in stroke research.

The book provides an admirable review of current knowledge regarding experimental stroke research, and outlines the problems and some solutions in the clinical application of such knowledge. I think that this book will find a wide readership in both clinical and experimental stroke research, and will be useful reading for clinicians involved in stroke management. If I had a concern, it would be that the discussion of progress in clinical therapy seems more optimistic than justified. However, it might be argued that one of the prime functions of monographs such as this is to arouse and sustain enthusiasm.

DAVID MENON

CORRECTION

Edwards A D, Patel J, Azzopardi D. Prevention of acquired neurological impairment in the perinatal period. *J Neurol Neurosurg Psychiatry* 1997;**63** (Supplement 1):S34-S38.

On page S35, in the left hand column, paragraph 3 the statement: "However, these data may be affected by sampling bias, as the patients who received magnesium *all* had a condition (pre-eclampsia) which has a protective effect on cerebral palsy in preterm infants . . ." should read: "However, these data may be affected by sampling bias, as the patients who received magnesium *sometimes* had a condition (pre-eclampsia) which has a protective effect on cerebral palsy in preterm infants . . ."